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A Technic for Isolation and Perfusion
of the Intact Canine Liver

Treatment of Whipple's Disease with Steroids

Massive Rectal Hemorrhage and Diverticular
Disease of the Colon

Editorial

Downgrading Gastroenterology

Twenty-sixth Annual Convention

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AMERICAN COLLEGE
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*The Pioneer Journal of Gastroenterology, Proctology
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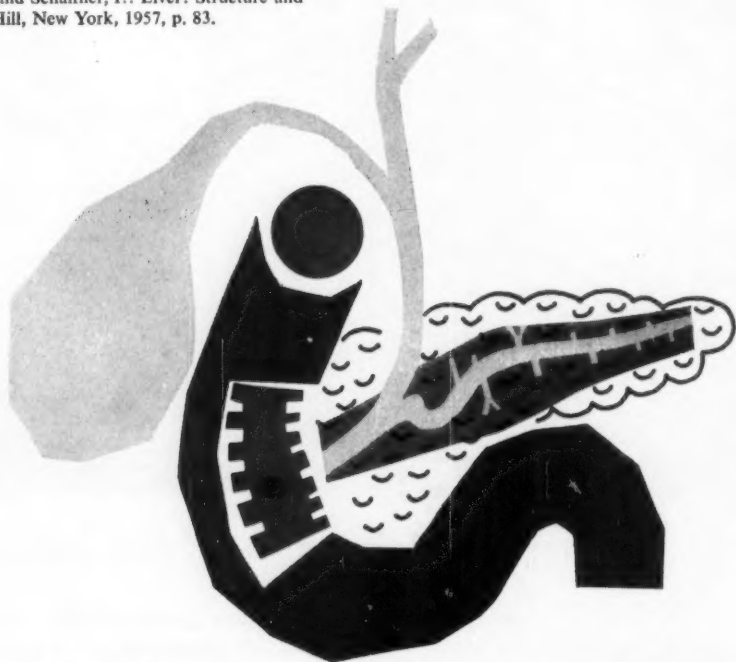
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NUMBER 1

A TECHNIC FOR ISOLATION AND PERFUSION OF THE INTACT CANINE LIVER

JOHN E. HEALEY, JR., M.D.*

Houston, Texas

For many years physiologists have attempted to isolate the liver of various animals so that they could study certain of the liver's metabolic activities. The achievement of this isolation requires an adequate perfusion method which

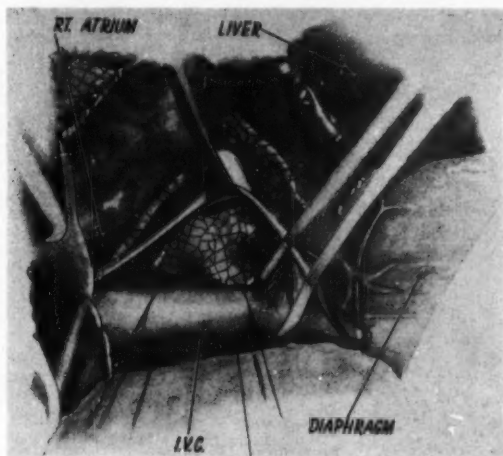


Fig. 1—Isolation of the segment of inferior vena cava (I.V.C.) from the diaphragm to the right atrium, showing the diaphragmatic incision and ligation of the phrenic vessels.

provides a continuous circulation through the organ, and an adequate supply of oxygen to the liver. McMichael¹⁰ in 1932, and also Bauer et al³, have described the historical aspects of such procedures. The isolation and perfusion

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This study aided in part by an American Cancer Society Institutional Grant.

of the liver have been possible in the past only by removing that organ from the animal's body. Andrews¹ described such a technic in detail.

Recent developments in extracorporeal circulation, a technic pioneered by Gibbon⁵, have revived interest in the isolation and perfusion of intact organs. Klopp⁷ suggested that an isolation-perfusion technic might be utilized in the treatment of patients with cancer, and the practical application of this suggestion was made by Creech⁴.

The perfusion method has since proven to be of some value in the treatment of patients with cancer of certain regions of the body, particularly, the extremities and pelvis. Subsequently, it was suggested that this also might

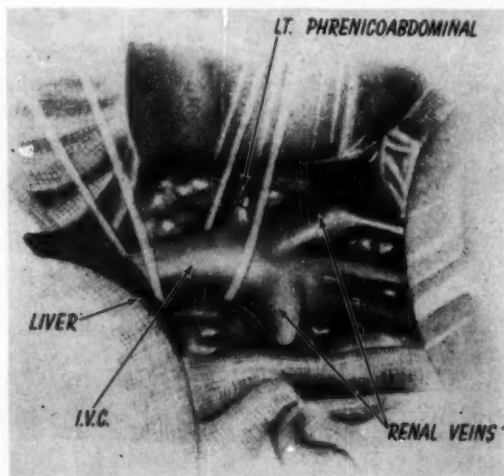


Fig. 2—Exposure of the inferior vena cava (I.V.C.) between the base of the liver and the renal veins. The left phrenicoabdominal vein is ligated. The right phrenicoabdominal vein is not shown.

provide a means whereby chemotherapeutic agents could be administered to specific organs. Since the liver is frequently involved in metastatic carcinoma, it was an obvious target in isolation perfusion. With this in mind, the investigation of the technic for isolation and perfusion of the intact canine liver was undertaken.

TECHNIC

These hepatic perfusion studies were carried out upon mongrel dogs varying in weight between 10 and 20 kg. Preoperatively these animals were given an intramuscular injection of penicillin and streptomycin. Demerol (2.5 mg.

per kg.) was administered as a preanesthetic agent and intravenous sodium pentobarbital (20 mg. per kg.), for initial anesthesia. An endotracheal tube was inserted, and inhalation ether given if supplemental anesthesia was required. The femoral vein was cannulated for infusion purposes, and the femoral artery, for continuous blood pressure monitoring. The electrocardiographic and electroencephalographic tracings were also continuously monitored on a multi-recording apparatus.

A thoracoabdominal approach is utilized; the abdominal incision extending from the xiphoid process to the umbilicus and the chest opened through either the seventh or eighth interspace, depending upon the configuration of the

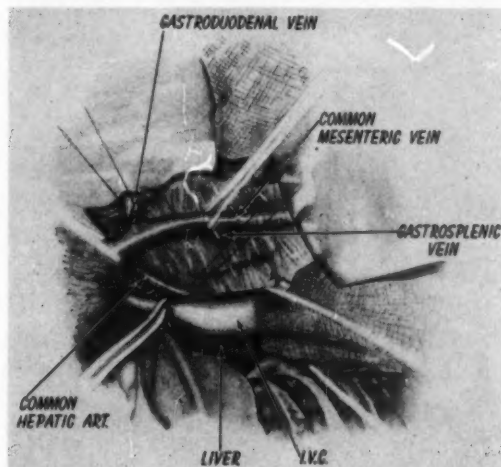


Fig. 3—Isolation of the portal vein from the union of the gastrosplenic and common mesenteric veins to the bifurcation of the vessel at the hilum of the liver. Its main tributary, the gastroduodenal, is ligated. Also shown are the two ligatures on the common hepatic artery; one at its origin from the celiac axis and the other beyond the last proper hepatic branch.

animal. Just prior to the opening of the chest, oxygen is administered by an automatic respirator through the endotracheal tube. The diaphragm is incised from its xiphoid attachment to the orifice of the inferior vena cava. All phrenic vessels entering the inferior vena cava are occluded by suture ligatures.

Preparatory isolation of the vessels to be ligated or cannulated is next carried out. First, the segment of the inferior vena cava above the diaphragm is exposed and its only tributaries, the superior and inferior phrenic veins, were already ligated while incising the diaphragm. After freeing the vessel from the diaphragm to the cardiac entrance, two ligatures are placed in position, but not tied (Fig. 1).

Next, the inferior vena cava just below the liver is exposed. To gain adequate exposure of this vessel, it is necessary to sever the hepatorenal ligament. The right phrenicoabdominal vein entering this segment is ligated. This is a tedious procedure at times, because of the adherence of the adrenal gland to the posterior wall of the vein. A similar vessel entering the left side of the inferior vena cava, is then ligated. A tape is passed around the inferior vena cava at the inferior border of the liver, and another tape, just above the entrance of the renal veins (Fig. 2).

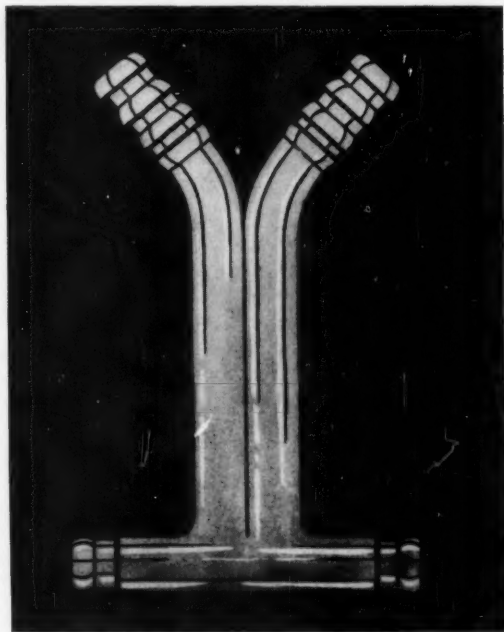


Fig. 4a—An illustration showing the special two-way cannula which is inserted into the inferior vena cava above the liver and into the portal vein.

The isolation of the portal vein is next carried out. Since no tributaries enter from the right side, dissection is confined to the vessels entering the left side of this vessel. The largest of these, the gastroduodenal vein, enters the portal vein high in the hepatoduodenal ligament and is ligated in continuity. One or two smaller tributaries may enter the portal vein, either above or below the gastroduodenal vein, and are likewise ligated. An umbilical tape is passed around the portal vein just below its bifurcation at the base of the liver, and a second tape, just above the union of the gastrosplenic and common mesenteric veins. The intervening portion of the portal vein is freed, care being taken not

to strip the peritoneal covering from its anterior surface, for this additional layer aids greatly in the repair of the vessel. Two cotton ligatures are then placed in position to secure the cannula which is to be inserted later (Fig. 3).

The proper hepatic artery in the dog is not a single vessel, but a number of vessels, anywhere from two to five, arising from the common hepatic artery as it arches under the *porta hepatis*. Therefore, to isolate the hepatic arterial supply, this artery—the common hepatic—must be ligated at two sites; first, at its origin from the celiac axis, and second, just above the pylorus proximal to

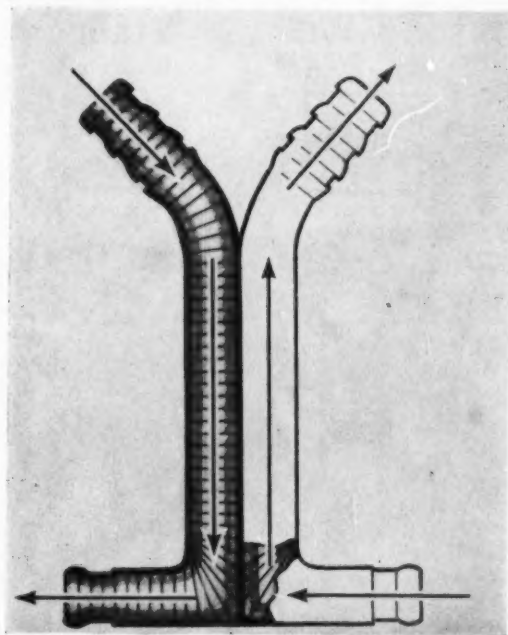


Fig. 4b—Diagram showing complete partitioning of the cannula.

the origin of the gastroduodenal branch. Ligatures are placed at these sites, but not tied (Fig. 3). The gastrohepatic ligament is then thoroughly examined for any possible aberrant arterial channels.

Following the exposure of these vessels, heparin (1.5 mg. per kg.) is administered intravenously, and the accessory apparatuses prepared. The latter includes a sigmamotor pump for the by-pass of the portal and caval flow to the right atrium and a pump-oxygenator which is utilized to perfuse the liver during its isolation from the general circulation. The sigmamotor by-pass is composed of a ten inch segment of $\frac{1}{8}$ " latex rubber tubing, passing through

the pump and adapted at either end to fit short segments of 3/16" Tygon tubing which in turn receive the venous cannulae. The oxygenator is a simplified bubble oxygenator¹¹ especially designed to perfuse at a low pressure and low flow rate which is required in an isolated organ perfusion. The machines are primed with fresh donor blood; the by-pass requiring approximately 50 c.c., and the oxygenator, 250 c.c.

One of the major problems in our early experiments was to keep a sufficient amount of blood flowing into the right side of the heart to maintain

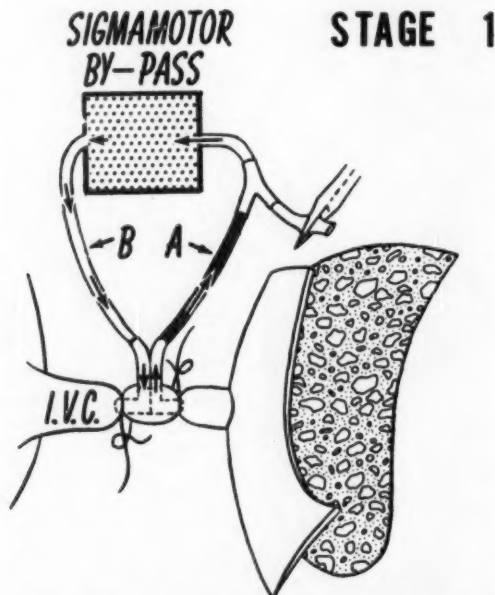


Fig. 5—Stage I of the isolation of the liver. Tube A is receiving all hepatic and caval blood below the diaphragm and tube B directs this flow back to the right atrium. I.V.C. inferior vena cava.

adequate cardiac function during cannulation of the vessels. It was found that this could be achieved most efficiently by dividing our cannulations into three stages.

Stage 1:—The inferior vena cava above the diaphragm is exposed and a clamp placed on this vessel at its entrance into the right atrium. A second clamp occludes the vessel at a point just above the diaphragm. A small incision is made into the inferior vena cava, and a specially made two-way cannula (Fig. 4) with attached tubing is inserted and secured by means of the previously placed ligatures. The tubing on the caudally directed end of the cannula

(Tube A, Fig. 5) is attached to the inflow tube of the sigmamotor pump, and the tubing on the cranially directed end (Tube B, Fig. 5) to the outflow of the sigmamotor. At the termination of this stage, all inferior caval and hepatic blood is shunted through the sigmamotor pump before returning to the right side of the heart. A very precipitant drop in blood pressure occurs during the occlusion of the inferior vena cava above the liver, but it quickly reverts toward normal when the by-pass pump begins operation. This cannulation procedure requires approximately three minutes and is the only period prior to perfusion that the blood flow from the lower portion of the body to the right atrium is interrupted completely.

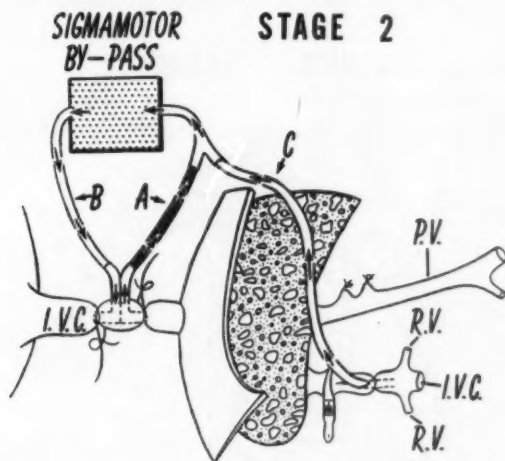


Fig. 6—Stage II of the isolation of the liver. Tube A now receives all hepatic flow and Tube C all inferior caval flow. P.V., portal vein; R.V., renal veins; I.V.C., inferior vena cava.

Stage II:—The inferior vena cava below the liver is then exposed. The tape placed around this vessel at the base of the liver is pulled taut and a bulldog clamp applied. The tape above the renal vein occludes the vessel at this level, and a small incision is made between the occluded points. A size 14 French catheter is inserted to the level of renal veins, and the distal tape tied over it. This catheter is immediately attached to the Y tube of the sigmamotor inflow (Tube C, Fig. 6). At the end of Stage II, therefore, Tube A contains all hepatic outflow, and Tube C all caval outflow below the diaphragm.

Stage III:—Exposure of the portal vein is next accomplished. The proximal and distal tapes are made taut to occlude the vessel, and an incision made midway between the tapes. A second two-way cannula with tubes attached is inserted and tied in place with the previously placed ligatures. The proxi-

mally directed tubing is designated as Tube D and the distal tubing as Tube E (Fig. 7). Tube E is now attached to the sigmamotor by-pass, replacing Tube A which in turn is attached to the inflow tube of the oxygenator. Tube D, leading to the portal vein, now functions as the outflow from the oxygenator. At this point the caval and portal blood below the liver is by-passed through the sigmamotor pump to the right atrium, and the liver is perfused by the pump-oxygenator via Tubes A and D. After the perfusion is started, the ligatures on the hepatic artery are tightened to obstruct that vessel and truly isolate the liver.

Perfusion may now be carried out for the desired period of time, which has ranged from 17 to 23 minutes in our survival animals. At the end of the

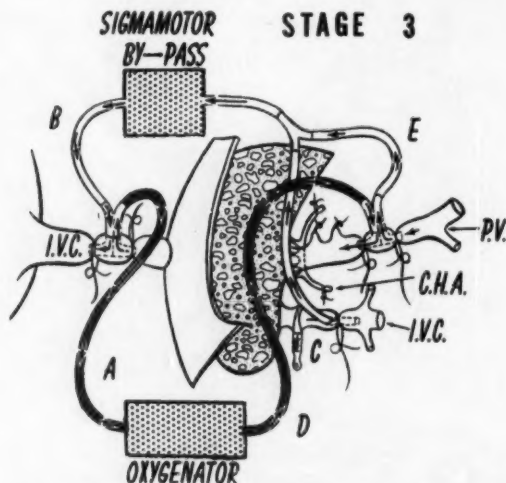


Fig. 7—Stage III of the isolation of the liver showing the final circuit for portal and caval by-pass and the liver perfusion circuit (See text). I.V.C., inferior vena cava; P.V., portal vein; C.H.A., common hepatic artery.

perfusion period, dismantling follows a sequence just opposite the procedure described above and is as follows:

Stage IV:—The ligatures on the hepatic artery are released. The inflow and outflow tubes of the oxygenator are clamped. The distally directed Tube E from the portal vein is clamped and removed from the sigmamotor by-pass and immediately replaced by Tube A. This reverts the circuit back to Stage II (Fig. 6). The retaining ties on the portal vein cannula are cut, and the cannula removed, while the proximal and distal tapes occlude the vessel. A modified Satinsky clamp placed over the incision in the portal vein allows portal flow to resume through the liver.

Stage V:—The inferior vena cava below the liver is again exposed, and a bulldog clamp placed over the caval cannula above the renal veins. The tape retaining the cannula is cut and the cannula removed. Again a modified caval clamp is placed over the incision in the vein, and the proximal and distal clamps are released allowing the inferior caval flow to resume through the sigmamotor by-pass as in Stage I (Fig. 5).

Stage VI:—Clamps are placed at the proximal and distal parts of the inferior vena cava above the diaphragm after the sigmamotor pump has been stopped. The retaining ties are cut and the cannula removed. A caval clamp is then applied, the proximal and distal bulldog clamps released, and the circulation re-established. Polybrene (2.0 mg. per kg.) is then injected intravenously to neutralize the heparin.

Following this, a leisurely repair of the three vessels may be carried out in the usual fashion with 5-0 arterial silk. The diaphragm is next repaired, following which the thoracic and abdominal incisions are closed in layers.

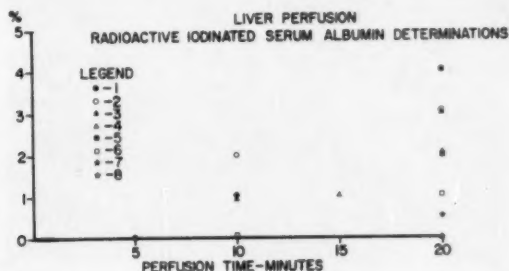


Fig. 8—Leakage from the isolation-perfusion circuit in eight animals as determined by RISA studies.

RESULTS

Control studies were carried out on five dogs to determine their tolerance to a thoracoabdominal approach and isolation of the involved vessels. All five of these animals survived.

A total of 21 animals were used in sacrifice experiments to solve the various problems that were encountered; such as, the type of cannulae to be used, the best site and sequence of cannulation, the perfusion rate feasible for this organ, the oxygen requirements, the development of an adequate by-pass mechanism, and a clamp which would prevent complete occlusion of the vessels during repair.

Using our present technic, we have done 10 experiments with five survivals, the last four being consecutive. Of the five deaths, three were small animals

whose portal veins were of such size that they became occluded following the repair of the incisions. One animal died due to cardiac arrest when the by-pass ceased to function due to an obstruction in the tubing by heart worms aspirated from the general circulation. The other fatality was due to hemorrhage from a poor technical repair of the portal vein.

Various biochemical studies were carried out on these animals, but the results are beyond the purpose of this presentation and will be presented in a future publication. One study of significance in regard to the isolation technic, however, was the leakage determination. A solution containing human serum albumin labeled with I^{131} (RISA) was injected into the perfusion circuit. Blood samples were taken from the by-pass circuit at intervals during the perfusion. These samples represented blood from the general body circulation and their RISA content was determined. As shown in Figure 8, the leakage ranged

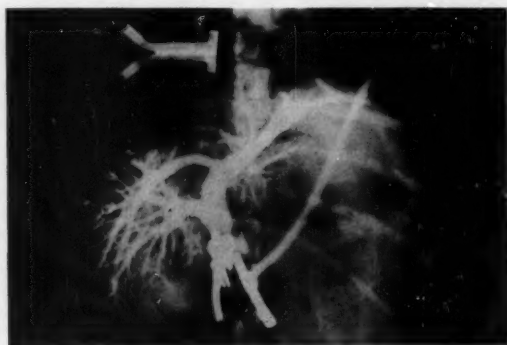


Fig. 9a—Serial portal venography revealing no escape to extrahepatic branches. Leakage in the case was zero per cent.

between zero and four per cent in eight of the animals in which the determinations were carried out.

In earlier perfusions we used another method, serial portal venography, to determine leakage from the perfusion circuit for we felt it was more important to know *where* the leakage was taking place rather than how much was leaking. An injection of 5 c.c. of a 60 per cent solution of Renografin was introduced into the circuit, and films were taken at the rate of two frames per second to detect any escape of the drug from the hepatic into the general circulation. By this method, we found that at times we were not ligating a left phrenic tributary of the inferior vena cava (Fig. 9). Since that time, we have done 15 perfusions in which this vein was routinely ligated. In 8 of these, leakage was reported as zero per cent and in 6, as less than one per cent at the end of 20 minutes. In the other case, RISA was given before the hepatic arteries were occluded and an 8 per cent leakage was reported.

Since the completion of the original series of 10 animals for attempted survival, we have performed 75 liver perfusions for various experimental purposes; such as, ammonia studies, studies to determine the tolerance of hepatic tissue to various chemotherapeutic agents, the study of intrahepatic vascular patterns and others. We feel now that the procedure is perfected to a degree that it may be tried on human cases with metastatic cancer.

COMMENT

One of the few publications presented in the literature pertaining to the perfusion of an *intact* canine liver was that of Ryan et al¹². These investigators passed a Foley catheter with perforations proximal to the bag up the femoral vein into the inferior vena cava until the bag was above the entrance of the hepatic veins. The tourniquet was then placed on the inferior vena cava above

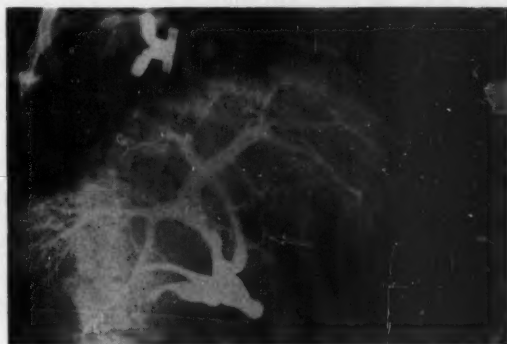


Fig. 9b—Another case in which a large vessel was observed outside the perfusion circuit (see arrow). This proved to be a left phrenic branch which communicated with the left phrenicoabdominal. Leakage in this case was reported as 28 per cent.

the renal veins. This catheter served as the inflow to the oxygenator. The outflow from the oxygenator was directed to the liver through a cannula in the portal vein. A by-pass circuit for caval and portal blood was established by a distally directed cannula in the portal vein, and a cannula placed in the inferior vena cava below the renal veins. The blood drawn through these catheters was shunted by an accessory pump to the internal jugular vein. No mention was made of the success or failure of this procedure.

Ausman and Aust² described a perfusion technic in which the outflow from the liver was so simply collected by a catheter placed in the vena cava under the liver. The inflow to the liver from the oxygenator was directed through the portal vein. No by-pass circuit for the portal and caval blood was described. Fifteen animals were so perfused with no deaths in the series. An alternate method was described for perfusion through the hepatic artery via

the splenic and the hepatic venous blood drawn through a catheter in the vena cava behind the liver. The aorta is then cross-clamped above the celiac axis.

Recently, Shingleton et al¹³ have carried out experiments on liver perfusions on dogs in which they cross-clamped the inferior vena cava and aorta above the diaphragm. The caval blood was drained through a catheter passed up the femoral vein to the inferior vena cava with a ligature placed above the renal veins, this served as the inflow to the perfusion circuit. The outflow entered a cannula in the portal vein directed toward the liver. Incorporated in the circuit was a controlled heat-exchange unit in five experiments, resulting in three successful perfusions. One experiment was under normothermic conditions, and this was also successful.

We do not feel that any of the procedures described above result in a true anatomic isolation of the liver. This fact is reflected in the leakage reported by Ausman and Aust and by Shingleton et al using the radioactive iodinated serum albumin method (RISA). Studies on the leakage factor during regional perfusions in other areas of the body have shown this method to be most efficient¹⁵. Using the portal vein for perfusion inflow, Ausman and Aust stated that they could obtain no better than two-thirds isolation of the chemical in a 20-minute perfusion. When perfusing through the hepatic artery, they reported a 15 to 32 per cent loss of the drug from the perfusion circuit. The leakage reported by Shingleton's group in four dogs using the RISA method has ranged between 10 and 20 per cent. Our leakage as determined by RISA studies in eight animals has averaged 1.9 per cent, ranging from zero to four per cent. This negligible leakage indicated that in utilizing this perfusion circuit for the administration of chemotherapeutic agents, the chief concern is the liver tissue tolerance to the drug. Whereas, in circuits allowing excessive leakage, consideration must also be given to the escape of drug into the general circulation when determining the dosage to be used.

We believe that our minimal leakage is due to the fact that all portal tributaries, particularly the gastroduodenal vein, are ligated prior to perfusion. Then too, the phrenic vessels are ligated as they enter the inferior vena cava above the diaphragm and the hepatic artery obstructed during the perfusion. In the other technics described, no mention is made of ligation of the phrenic vessels or of the portal vein tributaries.

Perfusion flow rates must be varied for each animal. As emphasized by Markowitz and Rappaport⁹, hepatic blood flow is not a static flow even in terms of rate of flow for a unit of liver or body weight, but varies with the physiological status of the organ. I do not feel that any definite statement can be made in regard to the flow rate required in any liver perfusion because of this individual difference. It is obvious, however, that flow rates necessary to maintain adequate oxygenation are lower than the estimated portal blood

flow reported in the literature. For example, Grindlay et al¹⁰ stated that the portal vein flow in dogs under pentobarbital anesthesia ranged between 145 and 505 c.c. per minute, a mean of 325 c.c. per minute. In some 50 liver perfusions which we have carried out to date, our highest flow rate was 325 c.c. per minute (30 c.c./min./kg.). In this case, as in four other cases in which the flow exceeded 15 c.c./min./kg., vascular congestion ensued with resultant liver enlargement and subcapsular hemorrhages. These changes occurred despite a good venous return. The flow rate must be regulated in each individual case depending upon the physiological state of the organ. We begin our perfusions at 10 c.c./min./kg. and alter the flow as the situation demands.

The line pressure in the perfusion outflow also is a variable factor and depends primarily upon the peripheral vascular resistance of the organ. We have never exceeded 110 mm. Hg. systolic pressure and have successfully perfused as low as 30 mm. Hg. When increased resistance is encountered, it is most likely due to the action of the various vascular sphincter mechanisms of the liver which have been so excellently reviewed by Knisely, Harding, and DeBacker⁸. The fact that these mechanisms must be considered during perfusion was shown very strikingly in one experiment. We started the perfusion at a flow rate of 115 c.c. per minute (10 c.c./min./kg.). To maintain this flow, 110 mm. Hg. line pressure was required. The liver became extremely engorged, and the venous return was poor. Papaverine (50 mg.) was injected into the circuit. The line pressure was immediately reduced, venous return improved, and the liver congestion was relieved. The use of papaverine in the circuit has been shown to be of value in overcoming increased peripheral vascular resistance in the perfusion treatment in other areas of the body, as well¹⁴.

Before any practical application can be made of this technic in the treatment of liver cancer in humans, very careful consideration must be given to the tolerance of the *normal* hepatic cells to the various chemotherapeutic agents. Work on dogs to study this phase of the problem has begun.

Aside from the importance of an isolation-perfusion technic as a method of approach to the chemotherapeutic treatment of patients with cancer of the liver, we feel it will be of prime importance as a physiological tool in the study of the various functions of the liver. As already mentioned, all previous physiological perfusion studies have been carried out upon livers removed from their normal environment. This technic, we feel, is the closest to a normal anatomic-physiologic arrangement thus far reported. We also hope to utilize this technic with a controlled hypothermia unit incorporated in the perfusion circuit during attempts at autotransplantation or homotransplantation of the liver.

SUMMARY

1. A technic is described for the isolation and perfusion of an intact canine liver.

2. The leakage from this circuit as determined by the radioactive iodinated serum albumin method has averaged only 1.9 per cent, signifying a tightly closed circuit.

3. The perfusion flow rate and the line pressure appears to be an individual situation depending upon the physiological status of the organ at the time of perfusion.

4. Such a perfusion technic may be utilized to study many of the physiological activities of the liver, to perfuse the donor liver during experimental transplantation of the organ, to administer chemotherapeutic agents in the treatment of carcinoma involving the liver, or perhaps, to administer drugs in the treatment of cirrhosis of the liver.

The author wishes to express his appreciation for the technical assistance given by Mrs. Christene Dinning, Mr. Stephen Gibson, and Mr. Peter Taylor.

REFERENCES

1. Andrews, W. H. H.: A technic for perfusion of the canine liver. *Ann. Trop. Med.* **47**:146, 1953.
2. Ausman, R. K. and Aust, J. B.: Isolated perfusion of the liver with HN_2 , *Surgical Forum* **10**:77, 1959.
3. Bauer, W., Dale, H. H., Poulsson, L. T. and Richards, D. W.: The control of circulation through the liver. *J. Physiol.* **74**:343, 1932.
4. Creech, O., Kremenz, E. T., Ryan, R. F. and Wimbald, J. N.: Chemotherapy of cancer: Regional perfusion utilizing an extracorporeal circuit. *Ann. Surg.* **148**:616, 1958.
5. Gibbon, J. H., Jr.: The maintenance of life during experimental occlusion of the pulmonary artery followed by survival. *Surg., Gynec. & Obst.* **69**:602, 1939.
6. Grindlay, J. C., Herick, J. F. and Mann, F. C.: Blood flow of the liver. *Am. J. Physiol.* **132**:489, 1941.
7. Klopp, C. T., Alford, T. C., Bateman, J., Berry, G. N. and Winship, T.: Fractionated intra-arterial cancer chemotherapy with methyl bis amine hydrochloride. *Ann. Surg.* **132**:811, 1950.
8. Knisely, M. H., Hardong, F. and Debuquer, H.: Hepatic sphincters: Brief summary of present-day knowledge. *Science* **125**:1023, 1957.
9. Markowitz, J. and Rappaport, A. M.: The hepatic artery. *Physiological Review* **31**:188, 1951.
10. McMichaels, J.: The portal circulation. I. The action of adrenalin pituitary pressor extract. *J. Physiol.* **75**:241, 1932.
11. Moore, E. B. and Healey, J. E., Jr.: A simplified perfusion pump for laboratory use, to be published.
12. Ryan, R. F., Wimbald, J. N., Kremenz, E. T. and Creech, O.: Treatment of malignant neoplasms with chemotherapeutic agents utilizing a pump oxygenator: Techniques and early results. *Bull. Tulane M. Fac.* **17**:133, 1958.
13. Shingleton, W. W., Reeves, J. W., Keppel, R. A., Mahaley, S. and Taylor, H. M.: Studies on abdominal organ perfusion for cancer chemotherapy. *Ann. Surg.* **151**:741, 1960.
14. Stehlin, J. S., Clark, R. L., White, E. C., Smith, J. L., Griffin, G. C., Jesse, R. H. and Healey, J. E., Jr.: Regional chemotherapy for cancer: Experiences with 116 perfusions. *Ann. Surg.* **151**:605, 1960.
15. Stehlin, J., Clark, R. L., White, E. C., Healey, J. E., Dewey, W. and Beerstecker, S.: Leakage factor in regional perfusion with chemotherapeutic agents. *A.M.A. Arch. Surg.* **80**:934, 1960.

TREATMENT OF WHIPPLE'S DISEASE WITH STEROIDS

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Although Whipple's disease was adequately described both clinically and pathologically in 1907, there have been fewer than 100 cases diagnosed either antemortem or postmortem. The gross pathology, and especially the histology of the disease, are highly characteristic and easy to recognize, so it must be concluded that Whipple's disease is extraordinarily uncommon. This case is reported because it is a typical example of this disease, and because it provides evidence concerning its treatment with steroids.

CASE REPORT WITH AUTOPSY

A 67-year old white man, a native Kansan, was admitted to the Halstead Hospital 13 February 1957. He stated that he had not been well since the previous summer; his appetite was poor and he had lost 16 pounds of weight. Recently he had had night sweats and increased perspiration; he was chronically tired and uninterested in carrying on his usual activities. He complained also of a persistent dull ache in his abdomen from the epigastrium down to the suprapubic area. He was suffering from constipation, not requiring treatment.

Physical examination revealed a tall, thin man who appeared chronically ill and anxious. The pulse was 80, regular; blood pressure 130/80; chest and abdomen were normal—no tenderness, no masses—and none of the abdominal viscera could be palpated. Rectal examination was negative; the prostate was normal. There were bilateral inguinal hernias; a 1 plus bilateral ankle edema was present. The clinical impression was: probable intraabdominal carcinoma.

In the hospital the patient was found to have an irregular temperature varying from 98° to 101°; his weight was 127 pounds. The following studies were done from 14 to 16 February: the chest x-ray was within normal limits; the KUB film showed no abnormalities; the gallbladder x-ray was normal; the barium meal examination revealed no abnormalities; proctoscopic examination to 10 inches was normal, and the barium enema examination was normal. Urinalysis was normal. Hemoglobin was 12 gm. per cent; hematocrit, 37 per cent; WBC, 7,600; the differential smear was normal with a moderate eosinophilia, which on four separate instances was 7, 13, 2 and 9 per cent. The sedi-

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mentation rate varied from 46 to 105 mm. per hour. The Ewald test revealed achlorhydria; prothrombin time was normal; platelet count, 198,000; thymol turbidity, 1.3 units; cephalin flocculation, negative; total protein, 5 gm. per cent; serum albumin, 2.6 gm. per cent; serum globulin, 2.5 gm. per cent; serum cholesterol, 180 gm. per cent; and alkaline phosphatase, 4.8 units. On 25 February cystoscopy and retrograde pyelograms revealed no abnormalities of the urinary tract.

On 2 March a chest x-ray showed a small pleural effusion on the right side. A diagnostic thoracentesis was done; a few atypical cells were found in the smears of the fluid. Bone marrow was obtained and the bone marrow was hyperplastic. The myeloid-erythroid ratio was 2:1. There were no abnormal white cells; no tumor cells were seen. The impression was: very active erythroid bone marrow. Esophagoscopy and bronchoscopy revealed no abnormalities.

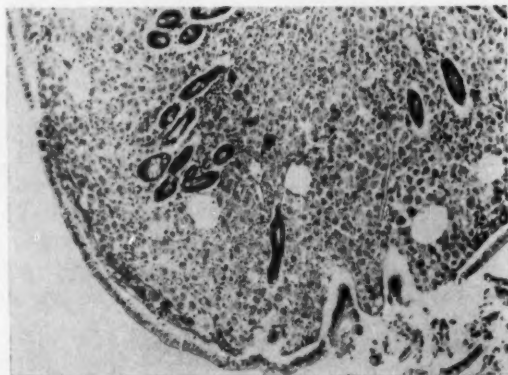


Fig. 1—Jejunum autopsy specimen. The *lamina propria* contains masses of large mononuclear cells with foamy granular cytoplasm. The empty spaces contain neutral fat. $\times 160$.

Abdominal exploration was carried out on 18 March. At operation a small amount of free fluid was present in the peritoneal cavity. This had a dusky, greenish appearance, but was not purulent and had no odor. Palpation of the intraabdominal contents revealed no abnormalities except in the first two loops of the jejunum. There were numerous visible lacteals in the wall of the jejunum, which seemed to be filled with a yellowish-gray substance in a nodular pattern; the mesentery of these two loops of jejunum was filled with firm nodules of discrete, easily movable, yellowish-gray material. These nodules varied in size of from one to four cm. There were similar nodes in the retroperitoneal area extending upward along the aorta toward the diaphragm. Several nodes were removed from the mesentery of the first loop of the jejunum for biopsy. A frozen section was interpreted as providing histological evidence of a lipogranuloma of Whipple's disease. The final microscopic study of these nodes was as follows:

the nodes consisted partly of lymphoid tissue with many irregular spaces surrounded by macrophages, some of them with large nuclei. Between the spaces there were large groups of foam cells which had distinct cell borders, a foamy cytoplasm and small nuclei. The smallest nodes had no fat spaces but consisted of lymphoid tissue and groups of very large macrophages with a foamy cytoplasm.

The patient made a rapid recovery from the laparotomy and received a short course of ACTH in the hospital. He went home on 31 March on prednisone 10 mg., four times daily for one week, to be followed by 20 mg. daily thereafter. The patient did well at home and by 12 June weighed 147 pounds. He was essentially asymptomatic and physical examination was normal.

In October of 1957 the patient weighed 156 pounds and had felt well since his surgery except for a short period of arthralgia and arthritis, apparently re-

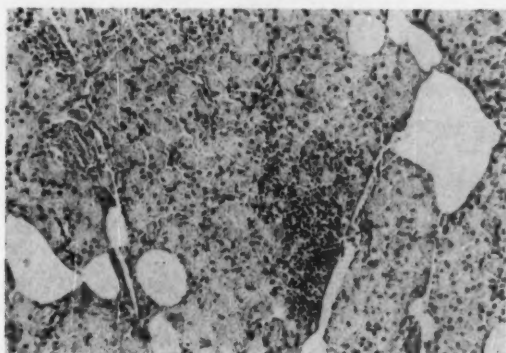


Fig. 2—Lymph node, mesentery of jejunum. Autopsy specimen. Large mononuclear cells replace normal lymph node tissue. Empty spaces contain neutral fat. $\times 160$.

sponding to an increased dose of prednisone in August. In October 1957 he was still taking 5 mg. prednisone daily. In January 1958 he complained of diarrhea for three to four weeks, with a loss of appetite. His weight was 132 pounds, a weight loss of 24 pounds; he was weak but had no localizing symptoms. Physical examination was not remarkable. The hemoglobin was 13 gm. per cent; hematocrit, 45 per cent; WBC, 8,100; eosinophils, 4 per cent; differential smear, normal; sedimentation rate, 13 mm. Examination of the stool qualitatively revealed an excess of fatty acids and fatty soaps. Prednisone was increased to 10 mg. four times daily; the dietary fat was restricted. A week later a maintenance dose of 5 mg. four times daily was established. By March 1958 the patient had deteriorated further; his weight was 121 pounds and there was increased diarrhea. Physical examination revealed a brownish discoloration of the skin, emaciation and 3 plus edema of the ankles. Serum cholesterol was 122 mg. per cent;

sedimentation rate, 30; hemoglobin, 7.5 gm.; hematocrit, 24 per cent; WBC, 7,750; differential smear, normal; serum albumin, 2.7 gm. per cent; serum globulin, 2.5 gm. per cent. This very weak emaciated patient died suddenly 27 March four days after admission to the hospital.

AUTOPSY FINDINGS

A postmortem examination revealed the following gross findings: A hemorrhagic infarct was found in the base of the left lung, a smaller infarct in the base of the right lung; the lower branches of both pulmonary arteries contained adherent thrombi. The heart weighed 420 gm. and was covered with fibrous adhesions; no infarcts were seen. The left coronary artery was completely occluded about 2 cm. from its origin; its wall was calcified and there was a central

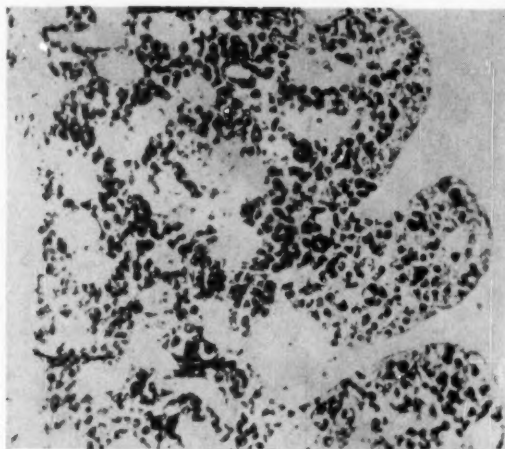


Fig. 3—Jejunum autopsy specimen stained with periodic acid-Schiff reagent. Epithelial elements are desquamated; postmortem changes. The mononuclear cells contain much periodic acid-Schiff positive material. x 160.

gray occlusion. The right coronary artery had a very narrow lumen with calcifications in its wall.

There were many adhesions around the spleen; the spleen was covered with a whitish membrane and weighed 250 gm. The liver weighed 1,900 gm. The mesenteric lymph nodes were very large and firm. They had a yellow cut surface and their diameter was .5 to 2 cm. The intestinal mucosa was edematous and hyperemic. There were yellow areas visible. The adrenal glands were small, weighing 5 and 6 gm.; the kidneys were grossly normal. The aorta was calcified in many areas and ulcerated. In the right iliac vein extending into the vena cava was a large thrombus with striations.

On microscopic examination a focal fibrosis of the myocardium with a chronic pericarditis was found. The thrombi in the pulmonary arteries and the iliac vein were antemortem in type. The coronary arteries showed an obliterative arteriosclerosis. The adrenal glands showed marked atrophy of the cortex with depletion of lipid. There was vacuolation of the cells of the *zona fasciculata*. The *z. glomerulosa* was almost completely absent and the *z. reticularis* was also atrophic. The medullary portion was well preserved.

A section of the stomach showed a normal mucosa; the mucosa of the colon was normal and there were no xanthoma cells. Sections of the jejunum and ileum showed polypoid thickening of the mucosa because of the presence of many foam cells. These cells infiltrated the entire mucosa beneath the epithelium. They were large, had a foamy cytoplasm and a small nucleus. Multiple sections of the lymph nodes from the mesentery showed only a few remnants of lymphoid tissue. Most of the glands consisted of sheets of foam cells in various stages of degeneration, with large empty spaces presumably filled with fat. The periodic acid-Schiff reagent stained the cytoplasm of the foam cells in both lymph nodes and the mucosa of the small intestine.

COMMENT

The histological findings in Whipple's disease are very striking. As in the case described above it is characteristic that the *lamina propria* of the small intestine and the mesenteric lymph nodes show a striking accumulation of large foamy-appearing pale staining cells with small nuclei. These same tissues are honeycombed with small and large pockets of neutral fat. The large mononuclear cells do not contain unusual amounts of lipid but do contain a mucopolysaccharide which can be stained with the periodic acid-Schiff reagent. These cells may also be found in lymph nodes in widely scattered regions of the body including peripheral lymph nodes, although regularly and grossly they infiltrate the mesenteric lymph nodes of the small intestine.

From the clinical standpoint the patients are often middle aged males who present with a chronic illness having with a variable degree of intensity, the symptoms and laboratory findings of a malabsorption syndrome. They have lost weight and strength and have usually had episodes of arthralgia. Frequently they have a brown pigmentation of the skin and hypotension. The course of the disease often is intermittently febrile and may be accompanied by generalized lymphadenopathy. At death the patients frequently have a panserositis which does not manifest itself prominently during life; apparently large effusions do not occur. From the clinical standpoint the disease cannot be distinguished with certainty from other diseases of the small intestine which cause the malabsorption syndrome. At laparotomy the findings are characteristic and since often there are gross pathological changes, one suspects that the disease has been present months or years prior to surgery. Twice now, brothers with this disease

have been reported. Gross et al¹ reported two brothers, one diagnosed at the age of 62, the other at the age of 63, both by laparotomy. Puite and Tesluk² reported brothers with Whipple's disease, one of whom died at the age of 27, the other at the age of 35. Both had characteristic findings on postmortem examination. It seems most unlikely that this rare disease could occur in brothers by chance. The possibility exists that Whipple's disease is familial and hereditary, and is due to an inborn error of metabolism. I am sure that the infrequency with which the disease has been diagnosed during life has made it difficult to carry out important biochemical studies. These are needed and it might be wise in the future to direct patients with this disease to institutions which are capable of carrying out major biochemical studies in the hope that basic information will provide a better understanding of the disease and possibly an improvement of treatment.

From the review of evidence to date it would seem that although the use of steroids in treatment has been reported upon favorably, only a temporary remission in the progressive downhill course of the disease can be expected^{1,15}. The remission may persist for months or years. It is peculiar and requires understanding that there are remarkable spontaneous remissions in the clinical state of the patient without, so far as can be determined, significant changes in the pathology. Patients have made dramatic improvement following a variety of maneuvers which have included laparotomy, psychotherapy, vitamin supplementation, antibiotics, and more recently the corticosteroids. I have the impression that the corticosteroids influence the status of the patient in relationship to his disease more profoundly than the other modes of treatment which have apparently led to good results in isolated occasions. In such instances it would seem that the corticosteroids do not influence the disease process itself, but rather exert a nonspecific effect producing an increased sense of well being, an increased appetite with consequent weight gain, and may exert some influence over the malabsorption syndrome and the symptom of diarrhea. The polyserositis may be influenced favorably.

On the other hand Gross et al¹ who have published a thorough study of this disease note that their experience with steroid therapy in four cases has been disappointing. One patient had transient improvement on 100 mg. of cortisone daily over a period of one month, both symptomatically and as judged by fat intake and excretion studies. A relapse occurred while he was still on cortisone; approximately one month after cortisone therapy had been discontinued he improved spontaneously and this improvement continued over a period of three and one-half years. The second patient died without apparent benefit from 75 mg. of cortisone for 5 days or following ACTH. The third patient benefited temporarily from cortisone administered orally over a period of 65 days. The fourth patient showed no improvement on cortisone, prednisone and ACTH in large dosage.

It is impossible to say whether the variable results are due to such factors as dosage or kind of steroid used. It is also not known whether the stage of the disease has any relationship to the results which are obtained. Nevertheless, it would seem that corticosteroids or ACTH should be given in adequate dosage in the hope of provoking a clinical remission. The choice between large intermittent dosage and chronic moderate dosage cannot be made yet on a rational basis.

SUMMARY

The case history of a patient with the rare Whipple's disease is reported in detail. Treatment is discussed and our current understanding of the role of steroids in the treatment of this disease is presented. It would seem that corticosteroids or ACTH may provoke a clinical remission. In general this is not sustained and a downhill course is resumed after a variable period.

REFERENCES

1. Gross, J. B., Wollaeger, E. E., Sauer, W. G., Huizenga, K. A., Dahlin, D. C. and Power, M. H.: Whipple's disease: Report of four cases including two in brothers, with observations on pathologic physiology, diagnosis and treatment. *Gastroenterology* **36**:65-93 (Jan.), 1959.
2. Puite, R. H. and Tesluk, H.: Whipple's disease. *Am. J. Med.* **19**:383-400 (Sept.), 1955.
3. Story, R. D. and Sagild, U.: Whipple's disease (intestinal lipodystrophy) and serum glycoproteins. *J.A.M.A.* **152**:312-317 (23 May), 1953.
4. Jones, C. M., Benson, J. A., Jr. and Roque, A. L.: Whipple's disease: Report of a case with special reference to histochemical studies of biopsy material and therapeutic results of corticosteroid therapy. *New England J. Med.* **248**:665-670 (16 April), 1953.
5. Wallace, J. C.: Intestinal lipodystrophy (Whipple's disease); Case report. *Texas M. J.* **48**:771-775 (Nov.), 1952.
6. Lepore, M. J.: Whipple's intestinal lipodystrophy. *Am. J. Med.* **17**:160-164 (July), 1954.
7. Plummer, K., Weisinger, B. B., III and Caravati, C. M.: Successful corticotrophin (ACTH) therapy of Whipple's disease refractory to cortisone. *A.M.A. Arch. Int. Med.* **91**:784-791 (June), 1953.
8. Radding, J. and Fiese, M. J.: Whipple's disease (intestinal lipodystrophy): Review of the literature and report of a case successfully treated with adrenocorticotrophin (ACTH) and cortisone. *Ann. Int. Med.* **41**:1066-1075 (Nov.), 1954.
9. Schaffner, F. and Scherbel, W. D.: Whipple's disease; glycoproteins, lipoproteins and other biochemical studies before and after cortisone treatment. *Gastroenterology* **29**:109-119 (July), 1955.
10. Wang, Chan-I, Janowitz, H. D. and Adlersberg, D.: Intestinal lipodystrophy (Whipple's disease) amenable to corticosteroid therapy. *Gastroenterology* **30**:475-488 (March), 1956.
11. Scott, P. W. and Hosie, R. T.: Whipple's disease; case report. *A.M.A. Arch. Int. Med.* **100**:280-282 (Aug.), 1957.
12. Crane, J. and Aguilar, M. J.: Obliterative lymphangitis of the mesentery in Whipple's disease. *Gastroenterology* **32**:513-527 (March), 1957.
13. Cheers, W. C., Smith, A. G. and Ruffin, J. M.: Diagnosis of Whipple's disease by peripheral lymph node biopsy; report of a case. *Am. J. Med.* **27**:351-353 (Aug), 1959.
14. Castleman, B.: Case records of the Massachusetts General Hospital: Case 43131 (Whipple's disease). *New England J. Med.* **256**:612-617 (28 March), 1957.
15. Brodoff, M., Hoffman, W. A., DeLuca, V. A., Jr. and Spiro, H. M.: Intestinal lipodystrophy (Whipple's disease); diagnosis by small intestine biopsy tube. *J.A.M.A.* **171**:154-155 (12 Sept.), 1959.

CLINICAL EVALUATION OF LIBRIUM IN GASTROINTESTINAL DISEASES

PRELIMINARY REPORT

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The clinical evaluation of a new drug without double-blind studies and controls is difficult, and conclusions based on such studies may frequently be erroneous. Nonetheless, the clinical response of patients is of value in determining the effectiveness of the new medication as compared with previous ones, its

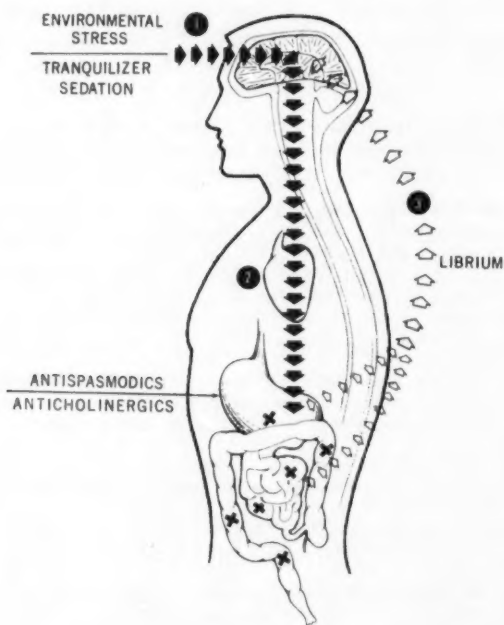


Fig. 1

proper dose, conditions in which it may be of help, intolerance, reactions to it, and contraindications for its use. Despite the pitfalls inherent in an uncontrolled study the response of patients, with various conditions, to a new and intriguing drug is always of interest.

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There is evidence that emotional tension may be a direct cause of gastrointestinal complaints¹ and an etiologic factor in some organic diseases of the gastrointestinal tract (duodenal ulcer and ulcerative colitis). Consequently we were interested in a drug that might relieve anxiety and secondarily also the resulting gastrointestinal distress. Preliminary reports on Librium†, a chemically new compound, which have indicated that it relieved anxiety without the usual sedative effect of many of the tranquilizers²⁻⁴ aroused our interest in its use in patients with gastrointestinal complaints primarily based on anxiety. The drug has been used in 120 patients, with adequate clinical evaluation in 90.

The patients selected for treatment were all seen in the Department of Gastroenterology primarily with gastrointestinal complaints. Anxiety, usually the cause of the symptoms, was the indication for therapy. A few patients had other conditions in addition to their gastrointestinal symptoms (obesity—3, tension or migraine headache—6, angina pectoris—4).

TABLE I
REACTIONS TO LIBRIUM IN 90 PATIENTS

Reaction*	Drug stopped	Drug continued (smaller dose)	Total
Depression	1	1	2
Sleepiness	2	3	5
Loss of libido	1	2	3
Ataxia and dizziness	1	2	3

*Five patients stopped the medication, and six continued on lower doses. Several patients had more than one reaction, i.e., depression and sleepiness; both occurred in several.

In 90 per cent of the patients, the usual dose employed was 10 mg. of Librium four times daily. A larger dose was required in 7 patients, who received 25 mg. three to four times a day. On this dosage, the drug was well tolerated with only a small number of reactions. Five patients stopped the medication because of side-effects, which consisted of marked sleepiness in 2, depression in 1, ataxia and dizziness in 1, and marked loss of libido in one woman. The latter patient reported that she did not want "housekeeping duties and responsibilities without bedroom privileges", and refused any further medication. Six other patients had similar side-effects, but continued on the drug at a lower dose. Reactions of depression and sleepiness disappeared in two patients when the dose was lowered; they ultimately obtained a good response, and subsequently tolerated the original dose. The undesirable reactions obtained are presented in Table I.

†Librium supplied by Hoffmann-La Roche Inc., Nutley, N. J.

Reactions to the drug, particularly sleepiness, appeared to be almost an "all or none" reaction. For example, those who complained of sleepiness developed it to an extreme degree; one patient slept for two days, another for 18 hours, while a third patient had to stop driving and sleep by the side of the road 45 minutes after taking the first dose. On the other hand, the majority of patients noted no sedative action at all, so that the sedative effect was either quite marked in the sensitive patient or entirely absent.

We were unable to relate the undesirable reactions to the age of the patients. While it might be anticipated that these side-effects would be more frequent in the aged, age made no difference in the incidence of reactions in this group (Table II).

TABLE II
RELATION OF AGE TO UNDESIRABLE REACTIONS

Age	No reaction			Reactions		
	Male	Female	Total	Male	Female	Total
20 - 29	1	3	4	0	0	0
30 - 39	5	7	12	1	2	3
40 - 49	17	9	26	2	2	4
50 - 59	13	7	20	1	2	3
60 - 69	4	7	11	1	0	1
70 - 79	4	0	4	0	0	0
Over 80	0	1	1	0	0	0

The reactions to the drug occurred shortly after the first dose, usually within 1 to 24 hours. The side-effects were not cumulative, and if we did not observe them within the first week, no reactions occurred.

The duration of treatment is shown in Table III. In addition to the 90 patients represented in the table, 30 others received the medication for too short a time to warrant evaluation.

The symptomatic response was evaluated as follows: 1. Excellent—completely asymptomatic, 2. Good—continued with some symptoms but considerable improvement, 3. Fair—some improvement but many symptoms continue, 4. Poor—no improvement at all. The response with respect to certain target symptoms in 85 patients who remained on the drug is shown in Table IV.

The patients with anxiety and anxiety reactions seemed to be helped more than other groups. The consistent response of these patients was that they felt

better, and irritating situations in their lives did not bother them as much as previously. Children still quarreled at home, work situations in the cases of executives were the same, but the patients were not disturbed and upset by these emotional crises as they had been before the medication.

The response of patients with mild depression was poor, the drug being of real help in only two of five patients. Since other reports have indicated its value in more severe depression, the poor response in this group may have been due to inadequate dosage.

Ten of 16 patients with anxiety with accompanying agitation (patients severely agitated by their anxiety, resulting in functional distress) were helped by the medication. Since these patients react to distress by developing anxiety and emotional crises, we do not know whether they had less distress, or whether the same distress did not evoke the same anxiety crises as before the medication.

TABLE III
DURATION OF TREATMENT

Duration	Number of patients
Less than one week	5
1 to 2 weeks	4
2 to 4 weeks	18
4 to 8 weeks	31
8 to 12 weeks	21
over 12 weeks	11

The response of patients with a true conversion neurosis (a defense mechanism that helps them solve their own life situation) was good in only two of seven patients. The poor results in patients with a conversion reaction was anticipated, and it is expected that the good response in two will be only temporary.

The drug was of help to 22 of 27 patients with chronic irritable colon (spastic colitis, mucus colitis, etc.) or with functional stomach distress (functional indigestion, hyperacidity syndrome, etc.). Nine patients with acute and chronic alcoholism associated with nutritional (Laennec's) cirrhosis were benefited. Four heavy drinkers, given Librium at the time of sudden withdrawal of alcohol, did not develop delirium tremens, although each had been such a heavy drinker that D.T.'s were expected. Librium seemed to help the patients tolerate acute withdrawal of alcohol.

Seven of 11 patients with abdominal parietal pain, thought to be of functional origin, obtained relief. One patient with pain of ten years' duration, that

was believed to be of a psychosexual etiology, obtained relief although she had not responded to many other medications. In contrast, another patient with a conversion reaction had obtained relief from her neuromuscular abdominal pain by local novocaine injections, but received no benefit from Librium.

We feel that frequently we can prognosticate with considerable accuracy the postgastrectomy syndrome in patients who undergo gastric resection. Those who develop the postgastrectomy syndrome are more anxious and apprehensive. On a trial basis, nine patients with postgastrectomy syndrome were given Librium with good results.

Too few patients with the remaining conditions were treated to warrant conclusive comment. Two patients with globus and one with glossodynia, previously resistant to treatment, did improve. Four patients with ulcerative colitis and three with regional enteritis felt more at ease and less tense on the medication. Three with functional vomiting and anorexia, and two with functional

TABLE IV
SYMPTOMATIC RESPONSE TO LIBRIUM—EMOTIONAL DISORDERS

Diagnosis	Excellent response	Good response	Fair response	Poor
Anxiety	18	33	3	3
Depression		2	2	1
Anxiety with agitation	5	5	3	3
Conversion neurosis		2	2	3

diarrhea, both thought to represent a conversion phenomenon were not appreciably benefited.

Nongastrointestinal conditions treated in which a good response was obtained include: generalized fibrositis syndrome (3), tension or migraine headache (5), obesity (3), angina (4), and hyperventilation syndrome with carpopedal spasm (1).

LIBRIUM WITH OTHER MEDICATIONS

Librium was frequently used concomitantly with other medications as in the patients with ulcerative colitis, regional enteritis, postgastrectomy syndrome, etc. For example, the combination of Librium with an appetite suppressor was most effective in three patients with obesity. One patient with functional vomiting and diarrhea obtained the best results from a combination of Librium, Compazine, and Lomotil. Tranquilizers, anticholinergics, appetite suppressors, etc., can be used in conjunction with Librium.

DISCUSSION OF POSSIBLE MODE OF ACTION

The mode of action of Librium is not clear. The possible mechanism of pain in patients with an irritable colon is represented diagrammatically in Figure 1. Colonic distress, cramps, or diarrhea may result from nervous or emotional stress in an environment which stimulates the psyche and results in increased vagal impulses discharged to the gut. The abdominal pain and distress further stimulate the psyche, resulting in more vagal discharges and greater colonic spasm. Thus a vicious cycle is started. Even in the absence of environmental stress, the cycle can be evoked by irritating foods causing a somatic response which in turn stimulates the psyche.

TABLE V

SYMPTOMATIC RESPONSE TO LIBRIUM—GASTROINTESTINAL DIAGNOSES

Diagnosis	Excellent	Good	Fair	Poor
Irritable colon and functional stomach distress	5	17	3	2
Acute alcoholism with nutritional cirrhosis	1	8	0	0
Abdominal parietal pain	3	4	1	3
Postgastrectomy	5	4	0	0
Duodenal ulcer	1	1	0	0
Glossodynia	1	0	0	0
Regional enteritis	0	3	1	0
<i>Globus hystericus</i>	2	0	0	0
Chronic ulcerative colitis	0	4	0	0
Functional vomiting	0	0	2	1
Functional diarrhea	0	0	2	0
Cardiospasm	0	0	1	0

Various types of medications can alter this cycle. Strong sedation to the point of causing sleep, as with the barbiturates eliminates the environmental stress by affecting the psyche. Tranquilizers presumably have the same action. Anticholinergic and antispasmodic drugs are effective to the extent that they block or modify the somatic response.

From our clinical studies, we believe that Librium may be effective by blocking the effect of the somatic response on the psyche and thus breaking the cycle. Librium may be effective by decreasing the patient's response to his disease without changing the basic condition, as for example in ulcerative colitis;

it may not change the inflammation in the colon, but enables the patient to tolerate his diarrhea, etc. better.

SUMMARY

Librium has been given with good results to 90 patients primarily with anxiety and functional gastrointestinal distress. Particularly good results were obtained in alcoholics with Laennec's cirrhosis and in patients with post-gastrectomy syndrome.

Reactions of sleepiness, depression, loss of libido, ataxia and dizziness occurred in 11 patients necessitating discontinuance of the drug in five.

These encouraging results suggest that further studies, employing the double-blind technic in patients with anxiety and gastrointestinal distress, are indicated.

REFERENCES

1. Brown, C. H.: The nervous patient with the nervous stomach. *J. Oklahoma M. A.*, 51:697-712 (Dec.), 1958.
2. Constant, G. A.: Preliminary report on the use of a new agent in depression and tension states. *Dis. Nerv. System* 21: Sect. 2, 37-39 (March), 1960.
3. Thomas, L. J.: Preliminary observation on the use of Librium (Ro 5-0690) in internal medicine. *Dis. Nerv. System* 21: Sect. 2, 40-42 (March), 1960.
4. Tickin, H. E. and Schultz, J. D.: Librium, a new quieting drug for hyperactive alcoholic and psychotic patients. *Dis. Nerv. System* 21: Sect. 2, 49-52 (March), 1960.

A CLINICAL EVALUATION OF AN ANABOLIC AGENT ADMINISTERED TO UNDERWEIGHT PATIENTS IN A GASTROINTESTINAL CLINIC

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A clinical evaluation was made of the efficacy of an anabolic agent to induce a gain of weight in resistant patients, attending a gastrointestinal clinic. The anabolic drug employed was Nilevar (17a-ethyl-17-hydroxyl norandosterone), a synthetic steroid analog of testosterone. The advantage attained in this compound^{1,2} was that it is only slightly androgenic being predominantly anabolic. Thus, by minimizing the strong virilizing effects commonly experienced with androgens, wider clinical application became feasible. Weston and his associates³ reported the favorable actions of Nilevar in reversing a negative nitrogen balance in a series of cardiac cases. Similar favorable results were obtained by Batson⁴ in patients afflicted with paralysis. Because of its ability to cause a retention of calcium, investigators have found this product useful in the therapy of osteoporosis⁵ and fractures⁶. Favorable anabolic effects have been demonstrated in pre- and postoperative care of patients⁷ and anabolic steroids have also been used to counteract corticosteroid catabolism⁸.

Significant favorable results were reported in the treatment of chronic underweight but otherwise normal adults by Kory and his co-workers⁹. They used the placebo technic type of study. Our investigation was confined to a similar problem of resistant underweight patients attending a gastrointestinal clinic. To vary the method of study, a high caloric diet was employed as a control instead of a placebo. This study was limited to the clinical observation of patients taking Nilevar orally, for a short-term period of two months in the majority of instances and a few for three months.

SELECTION OF CASES

Twenty-five adult patients attending a gastrointestinal clinic were investigated. They ranged in age from 27 to 69 years of age. Eleven were males and 14 were females. Patients were selected and only those who were abnormally underweight and stated that they could not gain weight on routine measures were included in this study. They ranged in weight from 77 to 124 pounds.

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Although their major concern was an underweight problem, the majority of individuals had a varying degree of anorexia, asthenia and a lack of vigor. Of the 25 patients studied, ten had an organic gastrointestinal ailment; 12 were diagnosed as functional dyspepsia; and three, just came to the clinic because they were underweight. The ten that had an organic disorder manifested gastrointestinal symptoms, such as the dumping syndrome, postcholecystectomy syndrome or diarrhea.

Before instituting therapy with the anabolic agent, disturbances which could be helped by specific measures were ruled out. These included such conditions as: glandular, psychogenic, toxic, diabetes mellitus, etc. The type selected for this investigation was characterized as an abnormally thin adult, with no specific recognized disease, except for some gastrointestinal complaints in the majority of instances, who had been unable to gain weight.

METHOD OF STUDY

Since an evaluation of the anabolic effect of this product was being made, it was important to establish a control study. All cases were therefore placed on a 3,000 calorie diet plus a vitamin-mineral supplement for two months. Then, the same patient was given Nilevar orally, 10 mg., three times a day for two months, and comparisons as to the efficacy of each mode of therapy were made. The individuals were observed approximately once a week and their weight, degree of appetite and sense of well being (vigor) were recorded. In addition, the cases were observed for any androgenic effects, for clinical evidence of jaundice, hepatomegaly, liver tenderness and for any side reactions.

RESULTS

The results of each type of therapy were recorded at the end of each two-month period (Table I). The response was graded as good, moderate or poor. The factors evaluated were the ability to gain weight, increase of appetite and the improvement of the sense of well-being. The gain in weight was considered good if it was within the range of 8-15 lbs., moderate within 3-7 lbs., and poor if it was 0-3 lbs. The grading of the effect in appetite and sense of well-being was based on the patient's subjective report.

EFFECT ON WEIGHT

In 25 cases, given a high calorie diet plus a vitamin-mineral supplement for a period of two months, the ability to gain weight was good in one; moderate in ten; and poor in 14; the mean weight gain for two months being 2.3 lbs. With the same patients for a similar period on Nilevar therapy, the response in weight gain was good in 12; moderate in eight; and poor in five, the mean weight gain for two months being 6.4 lbs.

EFFECT ON APPETITE

The individuals on a high calorie diet for two months showed little increase in appetite. The response was good in two; moderate in seven; poor in 16. For the same period on Nilevar therapy, the response was good in 11; moderate in 11; poor in only three.

EFFECT ON THE SENSE OF WELL-BEING

The improvement of the sense of well-being was similar to the appetite response. The high calorie diet produced a good result on only three; moderate response in eight; poor effect in 14. With the Nilevar therapy, on the other hand, the response was good in 15; moderate in seven; poor in three.

TABLE I

RESULTS OF THERAPY OF 25 UNDERWEIGHT PATIENTS WHO HAD BEEN UNABLE TO GAIN WEIGHT

	3,000 calorie diet plus a vitamin-mineral supplement treated for two months			Nilevar 10 mg. t.i.d. treated for two months		
	Response			Response		
	<i>Good</i>	<i>Moderate</i>	<i>Poor</i>	<i>Good</i>	<i>Moderate</i>	<i>Poor</i>
*Weight	1	10	14	12	8	5
	Mean	Weight Gain	2.3 lbs.	Mean	Weight Gain	6.4 lbs.
Appetite	2	7	16	11	11	3
Sense of well being	3	8	14	15	7	3

*Weight Gain
Good 7-15 lbs.

Moderate 3-7 lbs.
Poor 0-3 lbs.

It is apparent from this study that giving these patients a high caloric diet was of little help to them. They all had a poor appetite to start with and only Nilevar therapy was able to give them a real desire to eat and thus induce a good gain in weight in most instances.

In addition, the patients were observed for clinical evidence of jaundice, hepatomegaly, liver tenderness and any androgenic effects and for any side reactions. None of these was found.

LIVER FUNCTION STUDIES

Liver function tests were done in 25 cases after a minimum of two months of Nilevar therapy. The studies done were for icteric index, cephalin flocculation,

alkaline phosphatase, total serum proteins, serum albumin and globulins, total cholesterol and cholesterol esters. All results were within normal limits, except for two cases where there was a moderate reversal of the serum albumin/globulin ratio, prior to the initiation of therapy. In both instances, neither the high caloric diet nor Nilevar therapy altered these findings.

SUMMARY

Our investigation concerned itself with the clinical evaluation of Nilevar to induce weight gain in resistant cases. Twenty-five patients attending a gastrointestinal clinic were observed. Ten had evidence of gastrointestinal pathology, 12 were diagnosed as functional dyspepsia, and three just came to the clinic because they desired to gain weight. Cases were selected and only those who were abnormally underweight were included in this study.

The therapeutic factors evaluated were the ability to induce weight gain, increase the appetite and improve the sense of well-being. As a control, all cases were first placed on a 3,000 calorie diet plus a vitamin-mineral supplement for two months. Following this, they were then given, for a similar period, Nilevar 10 mg., three times a day.

The response to Nilevar therapy was much more pronounced than to a high caloric diet. Of 25 patients treated with the anabolic agent, a good gain of weight (7-15 lbs.) was observed in 14, an increase of appetite in 11 and a definite improvement in the sense of well-being in 15. On a high caloric diet, only one case showed a good gain of weight; two, an increase of appetite; three, a definite improvement in the sense of well-being.

In our study of 25 patients, 15 had no demonstrable pathology and 12 of these showed a good response. Of the remaining ten having gastrointestinal pathology, only two responded favorably. It is evident from this investigation that Nilevar fulfills a definite need in the short term therapy of the abnormally underweight adult and is more effective in those cases which have no evident gastrointestinal pathology.

REFERENCES

1. Saunders, F. J. and Drill, V. A.: The myotrophic and androgenic effects of 17-ethyl-19-nortestosterone and related compounds. *Endocrinology* **58**:567 (May), 1956.
2. McSwiney, R. R. and Prunty, F. T. G.: Metabolic effects of three testosterone derivatives including 17-ethyl-19-nortestosterone. *J. Endocrinol.* **16**:28 (Nov.), 1957.
3. Weston, R. E., Isaacs, M. C., Rosenblum, R., Gibbons, D. M. and Grossman, J.: Metabolic effects of an anabolic steroid, 17-alpha-ethyl-17-hydroxy-norandrostenone, in human subjects. *J. Clin. Invest.* **35**:744 (June), 1956.
4. Batson, R.: Clinical Investigators Report, Searle, 11 Feb. 1956.
5. Kessler, E., Flaherty, R., Cassidy, R., Nelson, W. P. and Nelson, S. S.: Metabolic effects of nilevar in osteoporosis: comparison of intramuscular and oral route of administration. *Clinical Research Proc.* **5**: No. 2 (April), 1957.

6. Kowalewski, K. and Morrison, R. T.: The effect of certain androgenic steroids on the uptake of radi sulphur in a healing fractured bone in the rat. *Canad. J. Biochem. & Physiol.* **35**:771 (Oct.), 1957.
7. Peden, J. C., Jr., Maxwell, M. D. and Ohlin, A.: Anabolic effect of a new synthetic steroid on nitrogen metabolism after operation. *A.M.A. Arch. Surg.* **75**:625 (Oct.), 1957.
8. Reifstein, E. C., Jr.: The rationale for the use of anabolic steroids in controlling the adverse effects of corticoid hormones upon protein and osseous tissues. *Southern M. J.* **49**:933 (Sept.), 1956.
9. Kory, R. C., Watson, R. N., Bradley, M. H. and Peters, B. J.: A six-month evaluation of an anabolic drug, norethandrolone, in chronically underweight individuals. *J. Clin. Invest.* **36**:907 (June), 1957.

MASSIVE RECTAL HEMORRHAGE AND DIVERTICULAR DISEASE OF THE COLON

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Reports during the past 10 years indicate that rectal hemorrhage is a fairly common complication of diverticular disease of the colon, that the incidence of massive hemorrhage is greater in patients with diverticular disease associated with arteriosclerotic vascular disease, and that surgical treatment is indicated if the bleeding is profuse or recurrent or cannot be controlled by conservative measures. The following report describes the occurrence and successful surgical management of massive rectal hemorrhage caused by diverticular disease in a patient with hypertensive cardiovascular disease.

CASE REPORT

A 66-year old housewife was admitted to Herbert C. Moffitt Hospital on 14 January 1957, because of massive rectal bleeding of 5 hours' duration. During the 5-hour period the patient had vomited green material which contained no obvious blood or coffee-ground material. She reported being constipated on occasion and having noted mild periumbilical aching during the week preceding admission; no other gastrointestinal symptoms were present.

Rectal bleeding had occurred on one occasion previously, in September 1955, and had persisted for 1 week, necessitating transfusion of 1,000 ml. of blood. Roentgenologic studies at that time showed no abnormalities in the upper bowel. Sigmoidoscopic examination was negative, but additional radiologic studies utilizing barium suspension enema and air for contrast had shown diverticula in the descending colon.

The patient had been admitted to Herbert C. Moffitt Hospital for the first time in December 1956 with a history of hypertension, atrial fibrillation and mild congestive heart failure of 18 months' duration, for which she had been treated with digitalis, low sodium diet and antihypertensive agents. Ocular examination at the time of admission showed Grade II K-W changes in the fundi. The heart was enlarged to the left; atrial fibrillation was present. The liver edge was 3 fingerbreadths below the right costal margin. Average blood pressure during the period of hospitalization was 160/100. Administration of reserpine and phenobarbital resulted in a fall in pressure to 140/90. After a

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2-week period of hospitalization the patient was discharged with instructions to take digitalis, phenobarbital and 0.4 mg. of reserpine daily. She was not seen again until the occurrence of massive rectal hemorrhage necessitated her admission to the hospital on 14 January 1957.

Physical examination:—The patient was a well-developed, slightly obese, white woman with cool, pale, moist skin. She had slight pretibial edema. The pulse was 64 and grossly irregular; blood pressure was 160/90. The ocular fundi showed Grade II K-W changes. The lung fields were clear to percussion and auscultation. The heart was enlarged beyond the anterior axillary line in the 6th left intercostal space. The abdomen was soft; there was slight tenderness in the right lower quadrant. The liver was 3 fingerbreadths below the right costal margin. The colon and abdominal aorta were palpated easily, but no abdominal masses could be felt. The bowel sounds were hyperactive. Except for dark red blood on the examining glove, no abnormalities were found on rectal examination.

Results of laboratory tests were: hematocrit, 37 per cent; white blood cell count, 6,500 per cu. mm. with 92 per cent polymorphonuclear leucocytes; routine urinalysis, normal. An electrocardiogram indicated atrial fibrillation and left ventricular hypertrophy.

Hospital course:—The patient passed bloody stools at increasingly frequent intervals. Despite replacement of 5,500 ml. of blood during the first 16 hours, the hematocrit dropped to 33 per cent. On palpation, the colon was found to be enlarged, dilated and boggy. No lesion could be detected by sigmoidoscopy to 23 cm. Roentgenologic studies showed multiple diverticula in the descending and sigmoid colon. Increasingly severe rectal bleeding necessitated replacement of 12,000 ml. of blood during the first 24 hours of hospitalization. By the 24th hour blood was being transfused at a rate of 1,000 ml. per hour, blood pressure was falling, and the pulse was rapid and thready. Because of the patient's rapidly deteriorating condition, an exploratory laparotomy was performed.

Operative and postoperative course:—No abnormalities were found in the stomach, duodenum, jejunum or ileum. The entire colon, however, was distended with blood, which had refluxed 2 feet into the terminal ileum. Multiple diverticula were found in the left side of the colon. One diverticulum, approximately 1 to 2 cm. in diameter, was entered by a large blood vessel and surrounded by an area of inflammation. No other abnormalities were found. The left transverse, descending and proximal sigmoid colon were resected. The right transverse and distal sigmoid colon were anastomosed. A tube cecostomy was performed to decompress the proximal colon. Immediately after ligation of the blood supply to the resected colon, the patient began to improve. The patient received 2,000 ml. of blood during the operation and an additional 1,000 ml. during the first 2 postoperative days. Improvement continued, and no further transfusions were required. The patient was ambulatory by the 7th postoperative day, and the

cecostomy tube was removed on the 8th day. She was discharged from the hospital 4 days later. When last seen 1 year after the operation, she had had no further episodes of rectal bleeding. Roentgenologic barium enema study showed a normal postoperative colon.

Pathologic examination of the resected portion of the colon showed numerous diverticula. The large diverticulum noted at the time of operation was indurated and the surrounding tissue showed both acute and chronic inflammatory changes. No site of bleeding could be demonstrated.

COMMENT

The incidence of rectal bleeding in diverticular disease has been studied in large series of patients. Noer¹, in an excellent review of 2,896 cases reported by 28 investigators prior to 1955, reported an 11 per cent incidence of rectal bleeding. In 4 other studies on a total of 568 cases, the incidence of bleeding was 23.4 per cent²⁻⁵. Combining the figures for the 5 series gives a total of 457 instances of rectal bleeding in 3,464 cases of diverticular disease, or an incidence of 13.2 per cent. The higher incidence in the more recent reports probably reflects the increasing awareness of this condition as a cause of rectal bleeding.

Massive rectal hemorrhage, similar to that observed in our patient, was noted in 41 of the cases reviewed by Noer and in an additional 42 cases reported in other studies⁴⁻⁷. As illustrated in the present case, patients with profuse rectal bleeding due to diverticular disease frequently have coexistent cardiovascular disease. Three of the 4 patients with diverticular disease and massive bleeding described by Hoar and Bernhard⁴ had a history of hypertensive cardiovascular disease. In Stanton's series of 14 similar cases⁵, 11 patients had one or more of the following conditions: arteriosclerosis, hypertension, cardiomegaly, congestive heart failure. Turnbull⁸ described massive rectal hemorrhage in 12 patients with diverticula of the colon and reported that all had arteriosclerosis; 5 also had arteriosclerotic heart disease and 3 had hypertension.

Conservative treatment, consisting of blood replacement, administration of sedatives and careful observation of the patient, has proved successful in the majority of cases of massive hemorrhage resulting from diverticular disease. To date, surgical treatment has not been used in a sufficient number of cases to permit evaluation of its effectiveness. Surgical procedures should be considered, however, in cases of persistent and profuse or recurrent hemorrhage or when necessary to permit diagnostic differentiation between carcinoma and diverticular disease.

The 14 patients described by Stanton⁵ were successfully treated by transfusion of 500 to 2,500 ml. of blood. In Quinn and Ochsner's series of 37 cases⁷, the bleeding was classified as massive in 23 patients (on the basis of hematocrit less than 30 per cent or the occurrence of shock, or both) and as moderate in

14 patients. Conservative treatment produced satisfactory results in 25 of their patients; one patient who was treated conservatively died from severe uncontrolled bleeding. In the remaining 11 patients surgical treatment was indicated by recurrent hemorrhage (8 cases), uncontrolled hemorrhage (1 case) and suspected carcinoma (2 cases). Four of the 8 patients who had recurrent hemorrhages were treated conservatively either because they refused to undergo an operation or were considered poor surgical risks. Of the remaining 7 patients who were treated surgically, 2 died postoperatively and 5 recovered without recurrence of bleeding. Kunath⁶ reported 3 cases of successfully treated rectal bleeding caused by diverticulosis. In 1 case bleeding was controlled by conservative measures; in the other 2 cases diverting colostomies were performed, following which bleeding ceased.

SUMMARY

A 66-year old woman with hypertensive cardiovascular disease was admitted to the hospital because of massive rectal hemorrhage caused by diverticular disease of the colon. Surgical treatment was successful in controlling the hemorrhage after conservative measures had failed. Diverticular disease as a cause of rectal bleeding and the association of massive bleeding in patients with diverticular disease and coexistent hypertensive and cardiovascular disease are recognized with increasing frequency.

REFERENCES

1. Noer, R. J.: Hemorrhage as a complication of diverticulitis. *Ann. Surg.* **141**:674, 1955.
2. Bokhair, L.: Diverticulosis and diverticulitis of the colon. *Quart. Rev. Surg.* **13**:75, 1956.
3. Fraenkel, G. J.: Rectal bleeding and diverticulitis. *Brit. J. Surg.* **41**:643, 1954.
4. Hoar, C. S. and Bernhard, W. F.: Colonic bleeding and diverticular disease of colon. *Surg., Gynec. & Obst.* **99**:101, 1954.
5. Stanton, A.: Massive hemorrhage due to diverticula of colon. *Am. J. Gastroenterol.* **24**:77, 1955.
6. Kunath, C. A.: Massive bleeding from diverticulosis of the colon. *Am. J. Surg.* **91**:911, 1956.
7. Quinn, W. C. and Ochsner, A.: Bleeding as a complication of diverticulosis or diverticulitis of the colon. *Am. Surgeon* **19**:397, 1953.
8. Turnbull, G. C.: Massive hemorrhage from diverticula of colon; report of 12 patients. *Quart. Bull. Northwestern Univ. M. School* **22**:292, 1948.

TREATMENT OF DIARRHEA IN IRRITABLE COLON, INCLUDING PRELIMINARY OBSERVATIONS WITH A NEW ANTIDIARRHEAL AGENT, DIPHENOXYLATE HYDROCHLORIDE (LOMOTIL)

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The irritable colon syndrome is a functional disturbance of the colon occurring in patients under emotional stress or tension¹. At least 75 per cent of patients with gastrointestinal symptoms suffer from this disorder. While the symptoms caused by disordered motility of the bowel—cramps, distention, flatulence, diarrhea or constipation—originate in the colon, the physician must recognize the fact that drug therapy alone cannot constitute complete management of the irritable colon syndrome, because tension and emotional stress are primary etiologic factors. By the same token, however, it is desirable that the patient be relieved of his distressing symptoms, such as diarrhea, so that anxiety and stress factors are diminished and the patient is less incapacitated in his daily life.

The purpose of this paper is to discuss the irritable bowel syndrome and to report preliminary results in patients with diarrhea due to irritable bowel syndrome treated with a new antidiarrheal agent. Diphenoxylate hydrochloride (Lomotil[®]) was administered to 35 patients who were diagnosed as having the irritable colon syndrome. Our purpose in conducting this study was to determine the effectiveness of this new compound in reducing transit time in these patients, thereby controlling their diarrhea.

ETIOLOGY

Both psychogenic and physiologic factors play important roles in the etiology of the irritable colon syndrome. Excellent studies have been reported by Grace² on the relationship of the parasympathetic nervous system to the tone, contractility, blood supply, secretions and excretions of the colon. The gastrointestinal tract responds to such stresses as anxiety, fright or resentment not only through the autonomic pathways involving the postganglionic nerve endings of the target organ or through the coordinating centers of the brain, but also through pituitary and adrenal activity. The colon responds to these stimuli with abnormal motility and irregular contractions causing areas of spasm and distention. This interference with coordinated propulsive function of the colon causes constipation if propulsion is slowed or diarrhea if propulsion is sped.

The underlying neurosis or tension from which these patients often suffer contributes to the physiologic disturbance of the colon. Many of them are compulsive eaters and consume excessive quantities of those foods which tend to

[®]Lomotil supplied by G. D. Searle & Co.

increase their distress—cabbage, spinach, onions, milk, fruit juices and carbonated drinks.

SYMPTOMS

One of the characteristic features of the irritable colon syndrome is the extreme lability of the symptom-complex. Patients suffering from this disorder often complain of headaches, lassitude, insomnia or backache in addition to those symptoms directly attributable to colonic disorder. Relief of one symptom is frequently followed by complaints of another. Such complaints may be outward manifestations of the patients' inner conflicts and tensions.

Abdominal distress, varying from vague discomfort to cramps, is common, with spasm or pain occurring soon after meals. The pattern of pain at times is constant and may suggest organic disease. When the pain is localized in the epigastrium, peptic ulcer may be suggested, while when the pain is in the right upper quadrant, gallbladder disease is simulated. Pain in the right lower quadrant often leads to a diagnosis of chronic appendicitis and left lower quadrant pain suggests diverticulitis⁴. These patients often have urgent watery or mushy stools. In female patients, menstruation is commonly a particularly difficult event, diarrhea being very common at this time. Fatigue, emotional upsets and cold drinks often bring on attacks of diarrhea which may be accompanied by a considerable amount of mucus. While diarrhea is not as common as constipation, it is more distressing and can be more disabling.

DIAGNOSIS

Although the patient's history is often suggestive of the condition, a diagnosis of irritable colon cannot be made unless organic disease has been excluded by appropriate physical, sigmoidoscopic, roentgen and laboratory examinations. Despite some reports to the contrary⁴, a barium enema examination is of the greatest importance. The capacity of the colon is much reduced and in many cases 15 ounces of barium will fill the colon entirely, in contrast to the average 38 ounces of barium required to fill the colon of the average normal patient⁵. The enema causes the patient considerable pain and he often has great difficulty in retaining it. The haustrations are numerous and deep-cutting and at times show many superimposed small, shallow wavelets, giving the bowel a serrated appearance⁶. The distal colon is often smooth, approaching the "band" or "tape" form seen in ulcerative colitis. The worm-eaten appearance of the colon characteristic of ulcerative colitis is, however, absent.

Since the symptoms of the irritable colon syndrome may mimic many organic disorders, it is necessary to weigh these symptoms carefully in differential diagnosis. Carcinoma and other tumors, peptic ulcer, hiatus hernia, gallbladder disease, ulcerative colitis, regional ileitis and diverticulitis must be excluded. Most cases of postcholecystectomy syndrome are probably caused by an irritable colon.

METHODS AND PROCEDURES

In this study, 35 patients who were diagnosed as having the irritable colon syndrome received diphenoxylate. Of the 35 patients, 17 were female and 18 were male. The patients ranged in age from 8 to 75 years. Prior to their diphenoxylate therapy, they had been maintained on such therapy as bland diets, paregoric, kaopectate, hydrophillic colloids, tincture of opium or belladonna.

Diarrhea was a serious problem for all of these patients. All patients were started on diphenoxylate therapy at a total daily dosage of 15 mg. This initial daily dosage was then decreased in 34 of the 35 patients to 5, 10, or 15 mg. daily, depending upon the response of the individual patient. The patients were then maintained on this reduced dosage for the duration of the study. All patients received 5 mg. tablets one, two, three or four times daily, as required. Some patients took the medication only when because of unusual stress the diarrhea was troublesome. No patient received more than 20 mg. per day or less than 5 mg. per day.

The shortest length of time for which any patient received diphenoxylate was 21 days; the longest, 120 days. The mean duration of diphenoxylate therapy was 73 days.

RESULTS

Twenty-six of the 35 patients (74 per cent) had excellent relief of their diarrhea, while the remaining 9 patients (26 per cent) had good results with diphenoxylate therapy. A patient was said to have had an excellent result only if relief from diarrhea was complete or was better with diphenoxylate than with all other drugs employed. A patient was said to have had a good result if relief from diarrhea was definite and moderate or if diphenoxylate was only as efficacious as any previous medication administered to the patient.

No side-effects of any kind were reported.

COMMENT

Drug therapy in the treatment of the irritable colon syndrome is based upon the concept that the primary symptoms, particularly the discomfort, cramps and diarrhea, are caused by the disordered motility of the bowel. Consequently, antispasmodics and, more recently, anticholinergics have been used extensively. While these drugs exert an effect upon bowel motility, there is no proof that they have any specific effect on the uncoordinated contractions which are thought to be the cause of the symptoms. When these drugs are effective, they diminish both normal and abnormal contractions to the same degree. The search continues for more effective antispasmodics, but little thought is given, apparently, to the fact that a drug accomplishing a full antispasmodic effect would cause a functional paralytic ileus⁷.

The entire question as to the use of drugs in the treatment of the irritable colon syndrome is complicated by the fact that, in this condition, psychosomatic factors are so important that it is difficult to assess the value of any drug. It is obvious, however, that these patients suffer from distressing somatic symptoms and require medical relief. Moreover, it is virtually useless to attempt to probe into the patient's emotional problems while he is in acute distress⁸. Stopping the patient's diarrhea is important, even though this is only a part of the total treatment. The physician should also help the patient to understand the cause and effect relationship of the day-to-day stress factors of his complaints. While the average physician has neither the time nor the experience to undertake extensive psychotherapy (nor is it frequently necessary), simple explanation and reassurance often produce gratifying results.

Since diphenoxylate is structurally related to meperidine, a study was conducted⁹ by Fraser and Isbell to determine the possible addicting potential of the drug. As a result of their investigation, these authors concluded that diphenoxylate has an addicting potential comparable to that of codeine. There was no evidence of withdrawal symptoms in any of the 35 patients in this study, nor would there seem to be any danger whatsoever of addiction in patients receiving therapeutic dosages of the drug. As means of discouraging deliberate over-dosage, however, diphenoxylate has been combined with subtherapeutic amounts of atropine sulfate in a single tablet.

SUMMARY

Thirty-five patients with the irritable colon syndrome received a new anti-diarrheal agent, diphenoxylate, for periods of from 3 to 17 weeks. Of these patients, 26 had excellent results while 9 had good results in relief of diarrhea. It must be remembered, however, that psychic as well as physiologic factors are involved in the etiology of irritable colon syndrome and that drug therapy without concomitant psychotherapy in some form is inadequate treatment.

REFERENCES

1. White, B. V., Cobb, S. and Jones, C. M.: Mucous colitis. Psychosomatic Medical Monographs No. 1, 1939.
2. Grace, W. J., Wolf, S. and Wolff, H. G.: Human Colon: Experimental Study Based on Direct Observation of Four Fistulous Subjects, New York, Paul B. Hoeber, Inc., 1951.
3. Kantor, J. L. and Kasich, A. M.: Handbook of Digestive Diseases, 2 ed. St. Louis, The C. V. Mosby Company, 1947, p. 324.
4. Kirsner, J. B. and Palmer, W. L.: Irritable colon. Gastroenterology **34**:491, 1958.
5. Kantor, J. L. and Kasich, A. M.: op. cit., p. 325.
6. Mills, R. W.: Roentgen-ray evidence of colonic secondary changes. Am. J. Roentgenol. **11**:487, 1924.
7. Posey, E. L., Jr., Barger, J. A., Dearing, W. H. and Code, C. F.: The effects of certain so-called antispasmodics on intestinal motility. Gastroenterology **11**:344, 1948.
8. Almy, T. P.: Reevaluation: What is "irritable colon"? Am. J. Digest. Dis. **2**:93, 1957.
9. Fraser, H. F. and Isbell, H.: Human pharmacology and addictiveness of ethyl 1-(3-cyano-3, 3-phenylpropyl)-4-phenyl-4-piperidine carboxylate hydrochloride (R-1132, Diphenoxylate), to be published.

BILE ACIDS AND DIOCTYL SODIUM SULFOSUCCINATE IN CONSTIPATION AND IRRITABLE COLON

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Because constipation is so frequently encountered in private practice and because constipated patients are willing but critical subjects, patients observed within the practice of internal medicine offer an excellent source of material for evaluating the efficacy of a drug or therapeutic regimen. Long-term close physician-patient relationship is best achieved in private practice. Even in this era of technological advancement the personal physician is still in a unique position to obtain important clinical data regarding the practical therapeutic action of drugs and perhaps most important of all, he is the one best qualified to determine a drug's "patient satisfaction" rating.

It is the purpose of this paper to review my experience with a combination of bile acids and dioctyl sodium sulfosuccinate as an adjunct in the management of private practice patients with problems of constipation and constipation associated with the irritable colon syndrome.

The therapeutic value of dioctyl sodium sulfosuccinate as a stool softener in the correction of constipation has been reported^{1,2,3}. Because of my previous favorable experience with dehydrocholic acid as a mild peristaltic stimulant in the treatment of chronic functional constipation^{4,5} I was interested in clinically evaluating a preparation of bile acids and dioctyl sodium sulfosuccinate (Dechotyl®-Ames) that became available for clinical trial in January, 1959. Each tablet contained dehydrocholic acid 200 mg., desoxycholic acid 50 mg. and dioctyl sodium sulfosuccinate 50 mg.

CLINICAL MATERIAL AND METHODS

Material:—One hundred nineteen patients were selected from my office practice of internal medicine—33 males and 86 females. Their ages ranged from 17 to 94 with an average age of 48. The patients were divided, according to the nature of their bowel dysfunction, into four groups.

Group I:—This group consisted of 75 patients with the major symptom of constipation.

Group II:—This was composed of 20 patients with symptoms of constipation and irritable colon.

Group III:—This group was composed of nine patients with symptoms of irritable colon without constipation. Three of these patients actually had recurrent episodes of diarrhea.

Group IV:—This included 15 patients with hemorrhoids but without constipation or other functional bowel disturbance. In this group it was desired to soften the stool and increase the ease of passage.

The duration of constipation in the 95 patients from groups I and II varied from six months to 60 years and the average duration of constipation was 15 years.

The patients in groups II and III initially had symptoms of bloating, flatulence, and abdominal cramping in addition to irregularity of bowel movement and abnormality of stool consistency. The nine patients in group III with irrita-



Fig. 1a

Fig. 1b

ble colon symptoms were included in this study to permit some evaluation of the efficacy and tolerance of bile acids and dioctyl sodium sulfosuccinate in patients with functional gastrointestinal disturbances unassociated with constipation.

Before receiving Dechotyl all patients were studied carefully. A complete history was taken to determine the importance of such factors as daily living pattern, diet, heredity, psychogenic disturbances and drugs. Histories were sufficiently thorough to be utilized as controls for individual patients. In 33 patients, constipation was attributable to drugs (antispasmodics and antihypertensives); in 20 patients, to diet (low residue or low calorie) and in nine patients, to a combination of diet and drugs (antacids, antispasmodics and ulcer diet). Fifty

of the patients had bowel movements only with the aid of various laxatives. Three patients had movements only with suppositories and 21 had movements only with enemas.

Physical examination, complete blood count and urinalysis were done on each patient, with proctoscopy, stool culture, protein bound iodine, and other

TABLE I
RESULTS OF BILE ACIDS AND DIOCTYL SODIUM SULFOSUCCINATE IN PATIENTS WITH
CONSTIPATION (GROUP I)

	Total patients	Excellent	Fair	Poor
Constipation (Group I)	75	67	6	2
Acute (< 1 year)	22	22	—	—
Chronic (> 1 year)	53	45	6	2
Ambulatory	72	65	5	2
Bedfast	3	2	1	0
Associated factors				
Postoperative	5	5	—	—
Drug-induced				
Antispasmodics	5	5	—	—
Antispasmodics + antacids	15	15	—	—
Antihypertensives	13	13	—	—
Diet-induced	20	20	—	—
Diet- and drug-induced	9	9	—	—
Fecal impaction	2	1	1	—
Biliary dysfunction	9	9	—	—
Ptosis of colon	7	6	1	—
Coronary disease	20	20	—	—
Pregnancy	2	2	—	—
Hypothyroidism	36	33	3	—

tests when indicated. Of the 119 patients, 15 had symptomatic hemorrhoids and two were pregnant. Thirty-six patients had laboratory evidence of hypothyroidism with protein bound iodine levels of 4 mcg. per cent or less.

Forty-six patients had complete gastrointestinal x-ray examinations (including cholecystogram, stomach and small bowel series and barium enema) to rule

out organic disease and to determine individual bowel patterns and motility prior to administration of Dechotyl. Previous anticonstipant therapy was discontinued prior to x-ray study so that a control pattern could be established. Three patients had previous cholecystectomy and six patients showed gallbladder dysfunction (poor concentration and poor contraction but no stones). Active duodenal ulcer was present in 10 patients and ptosis of the stomach and colon was noted in seven.

X-ray evidence of irritable spastic colon was observed in 20 patients with constipation (group II) and nine patients without constipation (group III). In all of these patients there was good clinical correlation with x-ray findings. No typical x-ray pattern was observed in patients with irritable colon syndrome. There was no evidence of atonic colon, a finding which is in agreement with Alvarez⁶, but also there was no hypermotility as was observed by Jordan in her patients⁷.

Method:—The general plan of the study was as follows: The patients continued all previous medication (for peptic ulcer, hypertension, hypothyroidism, etc.) without change except for discontinuing all laxatives, enemas and suppositories. Dietary habits and fluid intake were unchanged and the only change in therapy for functional colon dysfunction during the period of individual study was the addition of the bile acids and dioctyl sodium sulfosuccinate.

Prior to receiving the bile acids and stool softener and following a control period of at least one week during which all laxatives and enemas were discontinued, 38 patients had 24-hour barium meal x-ray studies of the colon. After three to 14 weeks of therapy with the bile acids and stool softener, the 24-hour barium meal x-ray studies were repeated. While the 24-hour film is unsatisfactory as a primary colon study, it does have an advantage over the barium enema x-ray in that it permits a study and objective comparison of motility of the barium and presence or absence of colon spasm prior to and following bowel therapy.

Regimen of therapy:—Initial dosage of the bile acid and dioctyl sodium sulfosuccinate preparation was two tablets daily (usually at bedtime). No adjustment of this dosage was necessary in 31 patients. After the initial effect of therapy was observed, to achieve the desired clinical results, dosage was increased in 50 patients and reduced in 38 patients. Seven patients with long established constipation required five tablets daily before achieving the desired clinical results, and one patient took as many as 12 tablets daily without result. The clinical effect of the combined bile acids and dioctyl sodium sulfosuccinate therapy usually developed rather gradually over two or three days (rarely as long as seven days), and occasionally when starting therapy, it was found helpful to increase the daily dosage temporarily. Dosage in these patients was then gradually decreased to two or three tablets daily. There was no evidence of cumulative effect or habituation to the bile acids and dioctyl sodium sulfo-

succinate; however, because of changes in the patient's diet or living habits, occasional adjustments in dosage were required. Thirty-four patients took the bile acids and dioctyl sodium sulfosuccinate for over 12 months without having to increase dosage. Thirty-six patients were able to stop the medication; however, 20 of these patients occasionally resumed therapy for a few days if stools became hard or infrequent. Three of these latter patients had not previously had a "normal" bowel movement for as long as they could remember.

Patients were followed for periods of from one month to as long as one year. Evaluation of the combined therapy was achieved by questioning the



Fig. 2a



Fig. 2b

patients at intervals of every one to two weeks. On the basis of relief of symptoms the clinical effectiveness was classified as "excellent", "fair", or "poor".

RESULTS

Group 1:—The results of bile acids and dioctyl sodium sulfosuccinate in the treatment of 75 patients with constipation are summarized in Table I. Sixty-seven (89 per cent) of the 75 patients receiving the combined therapy obtained excellent results with both subjective and objective improvement in bowel function. Frequency, consistency and ease of bowel movements were described by these patients as being nearly ideal. The six patients with fair results reported that while symptoms were partially relieved, they did not feel that the combi-

nation of bile acids and dioctyl sodium sulfosuccinate was any better than previously utilized laxative measures. The two patients with poor results had long histories of chronic constipation. One of these patients took as many as 12 of the bile acids and dioctyl sodium sulfosuccinate tablets daily without results.

Eleven of the patients in this group had previously received dehydrocholic acid tablets for treatment of constipation. When changed over to the bile acids and dioctyl sodium sulfosuccinate combination, nine patients reported that the number of tablets required was reduced by one-third to one-half, suggesting that the dioctyl sodium sulfosuccinate supplemented or potentiated the action of the bile acids. Two of the 11 patients, however, reported better results with dehydrocholic acid alone.

TABLE II

RESULTS OF BILE ACIDS AND DIOCTYL SODIUM SULFOSUCCINATE
PATIENTS WITH CONSTIPATION AND IRRITABLE COLON (GROUP II)
PATIENTS WITH IRRITABLE COLON (GROUP III)
PATIENTS WITH HEMORRHOIDS (GROUP IV)

	Total patients	Excellent	Fair	Poor
Constipation and irritable colon (Group II)	20	17	2	1
Irritable colon alone (Group III)	6	4	2	
Irritable colon with diarrhea (Group III)	3	3		
Hemorrhoids (Group IV)	15	13	1	1

That there were 36 patients with constipation and clinical hypothyroidism with low levels of protein bound iodine provides additional support to earlier reports that constipation and hypothyroidism frequently occur together. Constipation in these 36 patients had not been corrected by thyroid extract alone but was relieved by the addition of bile acids and dioctyl sodium sulfosuccinate.

Twenty patients with coronary vascular disease complicated by chronic constipation had excellent results with the bile acids and dioctyl sodium sulfosuccinate combination, thus avoiding the hazards arising from straining during defecation.

Group II:—The results of bile acids and dioctyl sodium sulfosuccinate in the treatment of 20 patients with constipation and associated symptoms of irritable colon are summarized in Table II. Seventeen (85 per cent) of the 20

patients obtained excellent results with bile acids and dioctyl sodium sulfosuccinate alone or in addition to previously ineffective antispasmodic medication and bland diet. The bile acids and stool softener therapy was given primarily for the relief of constipation, however, in 17 patients of this group the combined therapy was also helpful in relieving abdominal cramping, bloating and flatulence. Two patients in this group because of increased cramping had only fair results and one patient developed diarrhea.

Excellent results with bile therapy in the treatment of constipation and the irritable colon syndrome have previously been reported by Shallenberger and Kerr⁸.

Group III:—The results of bile acids and stool softener in the treatment of nine patients with irritable colon are summarized in Table II. Seven (78 per cent) of the nine patients in this group reported excellent results with the

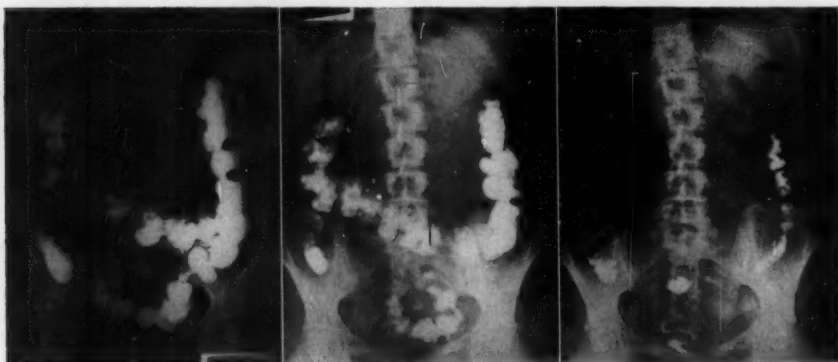


Fig. 3a

Fig. 3b

Fig. 3c

combined therapy. Four of these patients who had neither constipation nor diarrhea obtained complete relief of abdominal distress, bloating and flatulence, and the three other patients who had actual diarrhea due to irritability of the colon (up to three or four loose movements daily) had unexpected results in that diarrhea was controlled and symptoms of gaseous indigestion and abdominal distress were relieved. Two patients with the irritable colon syndrome reported only partial relief of symptoms.

Group IV:—The results of bile acids and dioctyl sodium sulfosuccinate in the treatment of 15 patients with hemorrhoids are summarized in Table II. These 15 patients had signs of bleeding and/or protruding hemorrhoids. While each patient had a daily bowel movement, straining or trauma aggravated the hemorrhoids. Treatment consisted of frequent sitz baths plus local therapy and the addition of the bile acids and dioctyl sodium sulfosuccinate to soften the

stool and increase the ease of bowel movement. Thirteen (87 per cent) of the 15 patients had excellent results, one patient had only partial improvement, and one patient developed intestinal cramping necessitating discontinuation of the bile acids and dioctyl sodium sulfosuccinate.

Results of 24-hour barium meal x-ray studies:—Twenty-four-hour barium meal x-ray studies were done in 38 patients, before and during therapy with bile acids and dioctyl sodium sulfosuccinate. For the most part there was good correlation between clinical improvement in bowel function and x-ray evidences of improved bowel motility, decreased volume of barium remaining in the colon and rectum, and decreased bowel spasm. Twenty-five of the patients x-rayed were from group I, ten patients from group II, and three patients from group III.

Figure 1 shows typical x-ray changes before and during therapy. The patient was a 51-year old man who had a bowel movement only every six to eight days (1a). X-rays were repeated after six weeks of treatment (1b), when he was having daily bowel movements with two tablets daily.

Figure 2 shows a similar marked decrease in 24-hour barium volume in a 56-year old man who had no bowel movements without laxatives or enemas, but with two tablets daily for two weeks had daily movements of normal consistency.

Progress in a 29-year old female who had no bowel movements without medication or enemas is shown in Figure 3. Figure 3a is a control film. After treatment with two tablets daily for one month, there was no improvement (3b). With three tablets daily she had regular movements with ease, the clinical improvement agreeing with the x-ray results (3c) one month later.

Side-effects:—Side-effects from the bile acids and dioctyl sodium sulfosuccinate were mild and infrequent, occurring in only five of the 119 patients (4.2 per cent). Three patients developed abdominal cramping and two other patients developed diarrhea, however, only two of these patients (one because of intestinal cramping and one because of diarrhea) were forced to discontinue therapy. Side-effects in the other three patients were mild and transient and the desired clinical effect was achieved with continuation of therapy. There was no evidence of toxicity or disturbance of nutrition, and there were no reports of increased flatulence or anal leakage. No "rebound" constipation with over-emptying of the colon occurred during therapy or at the time of stopping medication.

COMMENT

Although the concept of combining bile acids and dioctyl sodium sulfosuccinate for the treatment of constipation is relatively new, the use of bile acids and dioctyl sodium sulfosuccinate separately in the management of constipation has been established previously.

Bile salts and bile acids long have been used in the treatment of constipation. The writings of the ancients contain numerous references to bile; the earliest known reference is in an Egyptian sacerdotal papyrus written about 1300 B.C. where it is advised for use in enemas. It has long been known that bile has the particular characteristic of stimulating gut activity. Bile and bile acids acting through their natural channel, the intestinal mucosa, have a temporary local stimulating effect on the motility of the small intestine. Bile is apparently necessary in the intestinal tract for normal bowel movement⁹, and a number of investigators have referred to bile and bile acids as "physiological stimulants" or "normal laxatives" for the intestinal tract¹⁰⁻¹⁴.

Since its introduction to medicine in 1924, dehydrocholic acid (Decholin®-Ames) has been used primarily as a hydrocholeretic in the treatment of various biliary tract disorders. In addition, however, a number of physicians have reported the usefulness of dehydrocholic acid as a mild intestinal peristaltic stimulant in the treatment of constipation^{4,5,12}.

Desoxycholic acid is one of the natural bile acids and has a choleretic action thereby increasing the excretion of bile. In addition to stimulating intestinal peristalsis, desoxycholic acid promotes a more effective action of lipase by the emulsification of fats thus aiding the absorption of fatty acids and fat-soluble vitamins. The promotion of lipolytic action is important, as unsplit fats are reported to inhibit small bowel motility and contribute to constipation^{15,16}.

Dioctyl sodium sulfosuccinate is a synthetic detergent or wetting agent which lowers surface tension and enhances the penetration of fluids (water and lipids) into the feces thus softening and mixing the intestinal contents. Dioctyl sodium sulfosuccinate is neither absorbed nor altered chemically in the intestinal tract. Extensive pharmacologic and clinical studies indicate that it can be used orally in large doses over long periods of time without danger of toxicity or decreasing effectiveness. Large doses do not produce diarrhea^{2,17}.

The combination of bile acids and dioctyl sodium sulfosuccinate was found in this study of 119 patients with functional bowel disturbances to produce both subjective and objective relief of symptoms. The combination therapy gave excellent results in 84 of 95 patients with constipation that had previously responded temporarily or unsatisfactorily to various other forms of treatment. Sixteen of the patients responding to bile acids and dioctyl sodium sulfosuccinate had a history of having had no spontaneous bowel movement for as long as 60 years without enemas or suppositories. Thirty-six of the 95 patients with constipation achieved essentially normal bowel function and were able either to stop therapy completely or to use it only periodically. Most patients reported that the combination therapy gave them a normal comfortable bowel movement without abdominal cramping, flatulence or diarrhea. Most significant is the fact that bile acids and dioctyl sodium sulfosuccinate were successfully used in the treatment of 17 of 20 patients having constipation associated with the irritable

colon syndrome. Unlike other laxative preparations the bile acids and dioctyl sodium sulfosuccinate appeared to be well tolerated by the irritable colon.

Two pregnant patients with constipation obtained excellent results with this combination therapy. Bile acids and dioctyl sodium sulfosuccinate would seem to be a particularly logical combination for the treatment of constipation of pregnancy. Biliary stasis and hypercholesterolemia occur during the latter months of pregnancy and may be important to the probable correlation that exists between pregnancy and gallstone formation. Dehydrocholic acid is one of the most potent hydrocholeretics available and is helpful in relieving biliary stasis. Bile acids and dioctyl sodium sulfosuccinate have no effect on milk secretion or composition. Dehydrocholic acid and desoxycholic acid are excreted by the liver either unchanged or as taurine and glycine conjugates with the bile while dioctyl sodium sulfosuccinate is not absorbed from the bowel and does not appear in the body secretions. On the other hand, emodin cathartics such as cascara sagrada, senna, rhubarb, and aloe are partially secreted in the mother's milk, and during lactation, they may appear in the milk in sufficient amount to affect a nursing infant¹⁸. Bile acids and dioctyl sodium sulfosuccinate should be studied further in treatment of constipation of pregnancy.

SUMMARY AND CONCLUSION

In this study of 119 patients having either constipation, constipation associated with the irritable colon syndrome, irritable colon alone or hemorrhoids, it was found that a preparation of bile acids and dioctyl sodium sulfosuccinate gave results that were excellent or good in 104 patients (87.4 per cent), fair in 11 patients (9.2 per cent), and poor in four patients (3.4 per cent).

This combination therapy usually provided mild peristaltic stimulation and fecal softening. No toxicity was observed. Cramping and/or diarrhea in four patients (3.4 per cent) were the only side-effects noted, and only two of these patients had to discontinue the bile acids and dioctyl sodium sulfosuccinate because of side-effects.

While ultimate correction of constipation requires continued emphasis by the physician on the regulation of diet, fluid intake, regular hours of rest and exercise, and re-training of the bowel habits by going to stool regularly, this study has shown that combined therapy of bile acids and dioctyl sodium sulfosuccinate is a helpful adjunct to the constipation re-education program.

ACKNOWLEDGEMENT

I wish to thank N. M. Starkman, M.D., Chicago, Ill. for the roentgenologic interpretations, Daniel Streicher, M.D. and Irene Shafer, R.N. for the opportunity to include in this study patients at the Kenmore House Convalescent

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REFERENCES

1. Wilson, J. L. and Dickinson, D. G.: Use of dioctyl sodium sulfosuccinate (Aerosol O. T.) for severe constipation. *J.A.M.A.* **158**:261-263 (28 May), 1955.
2. New and Unofficial Drugs, 1960. A.M.A. Council on Drugs. Philadelphia, J. B. Lippincott Co., pp. 490, 491.
3. Friedman, M.: Dioctyl sodium sulfosuccinate (Doxinate) in chronic functional constipation. *Am. Pract. & Digest. Treatment* **7**:1588-1591, 1956.
4. Portis, S. A. and King, J. C.: The gastrointestinal tract in the aged. *J.A.M.A.* **148**:1073-1079 (29 March), 1952.
5. King, J. C.: Practical ambulatory therapy of functional constipation. *Am. J. Digest. Dis.* **22**:102-108 (April), 1955.
6. Alvarez, W. C.: The physiology of constipation. *Dis. Colon and Rectum* **1**:333-338, 1958.
7. Jordan, S. M.: Functional colitis and constipation. *Ann. N. Y. Acad. Sci.* **58**:377-379, 1954.
8. Shallenberger, P. L. and Kerr, P. B.: The irritable bowel syndrome. *Postgrad. Med.* **13**:32-38 (Jan.), 1953.
9. Horrall, O. H.: Bile, Its Toxicity and Relation to Disease. Chicago, University of Chicago Press, 1938, p. 180.
10. Haney, H. F., Roley, W. C. and Cole, P. A.: The effect of bile on the propulsive motility of Thiry-Vella loops in dogs. *Am. J. Physiol.* **126**:82-88, 1939.
11. Teeter, E. J.: Bile physiology and therapy. *J.A.M.A.* **131**:1482-1484 (31 Aug.), 1946.
12. Rafsky, H. A. and Honig, L. J.: Changes in the colonic function and use of laxatives in the aged. *Ann. N. Y. Acad. Sci.* **58**:513-518 (15 July), 1954.
13. Raddin, J. B.: The clinical problem of the constipated woman. *Med. Times* **86**:302-309, 1958.
14. Popper, H. P. and Schaffner, F.: Liver, Structure and Function. New York, McGraw-Hill Book Company, 1957, p. 84.
15. Best, C. H. and Taylor, N. B.: The Physiological Basis of Medical Practice, 5th ed., Baltimore, Williams & Wilkins Company, 1950, pp. 542-543.
16. Council on Pharmacy and Chemistry Report: Degalol (Desoxycholic acid). *J.A.M.A.* **117**:361 (2 Aug.), 1941.
17. Spiesman, M. and Malow, L.: New fecal softener (D.S.S.) in the treatment of constipation. *J. Lancet* **76**:164-167, 1956.
18. Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics, 2nd ed., New York, The Macmillan Co., 1956, p. 1050.

EDITORIAL

DOWNGRADING GASTROENTEROLOGY

On 15 June 1960 Kirsner¹ delivered an address at the annual meeting of the American Medical Association on "Specialization and Gastroenterology". He said in part that gastroenterology was uniquely endowed with many of the qualities of a comprehensive medical specialty. It offers unparalleled opportunity for clinical activity and for significant research. In gastroenterology the science and art of medicine are indivisibly combined. Gastroenterologic diseases encompass many problems of internal medicine and important aspects of surgery. He ably presented the historic opposition to specialization and defended the need for such an important specialty as gastroenterology.

A very excellent statement was prepared by the Committee on Education and Training of the American Gastroenterological Association. This was approved by the Governing Board of that Association, the Subspecialty Board of Gastroenterology and the parent American Board of Internal Medicine. It was sent to many of us on 8 April 1960 and was published in *Gastroenterology* in August 1960². It indicates very clearly and correctly that in the extremely broad and complex field of gastroenterology, programs for graduate teaching and training must provide comprehensive experience in many of its important subareas. The latter include the study and treatment of in- and outpatients with all types of gastrointestinal disorders, training in the basic sciences, special laboratory and endoscopic procedures, gastrointestinal radiology, surgical aspects of gastroenterology and original research in gastroenterology.

Despite the importance of gastroenterology as a subspecialty in medicine, and the constant need to improve the training program for residents and Fellows in this field, events have recently taken place which to my mind adversely affect the future of our specialty. In a letter dated 3 October 1960, sent by the Council on Medical Education and Hospitals to various institutions, and in the *Journal of the American Medical Association* of 8 October 1960³ there appear the following comments: "At the request of the American Board of Internal Medicine, the Council on Medical Education and Hospitals has agreed to discontinue approving residency training programs in the four subspecialties of internal medicine. The lists of approved programs in the medical specialties of allergy, cardiovascular diseases, gastroenterology and pulmonary diseases carry the captions that the programs listed are approved only until 30 June 1961. They will not be listed in future directories. New applications for approval of residency training programs in the subspecialties will no longer be accepted. The Board considers that candidates for subspecialty training are sufficiently mature to select their own type and locations for such training, and expects that candidates and institutions can plan the kinds of programs needed after study of the requirements for qualification published elsewhere. Further advice regarding subspecialty

training must be secured by correspondence with the Secretary of the American Board of Internal Medicine. In the 'Essentials of Approved Residencies' the sections on internal medicine will be revised at a subsequent date to remove any reference to separate residency in the subspecialties of allergy, cardiovascular diseases, gastroenterology and pulmonary diseases, other than as portions of residency programs in internal medicine. The Subspecialty Boards, however, are not discontinuing certification in these subspecialties. Requirements for subspecialty certification will be found published in detail in the appropriate section of this issue". I carefully scrutinized the Journal but could not find this appropriate section. In its place, on page 569, there appears the following comment! "Because of space restrictions the sections on Essentials of Approved Residencies for Certification of the American Specialty Boards were omitted. These sections will appear in bound volumes which are available upon request"³. As was noted above, however, the revision of these volumes will remove any reference to separate residency training in gastroenterology.

It is apparent that for the present the American Board of Internal Medicine intends to downgrade, but not eliminate training programs in gastroenterology. If this is not the reason then why did the Board request discontinuation of approval and listing of residency training programs? It is unrealistic to make the statement that candidates for subspecialty training are sufficiently mature to select their own types and locations for such training. Are not all young physicians seeking residencies in any field mature? Is the candidate who seeks a residency in Internal Medicine so immature that for him programs must be approved and listed? Who but men of standing such as those of the Committee on Education and Training of the American Gastroenterological Association, which recommended the features of adequate postgraduate training in gastroenterology, can decide which hospital training programs should be approved? Why should not such men guide our prospective applicants for training in gastroenterology, rather than leave it to the judgment of the applicant who would find it extremely difficult to find out for himself? And if such prominent educators approve a program, why should it not be listed in appropriate directories for the information of applicants? Are we justified in encouraging a young physician to spend a year or more in an institution where he feels that the training program is adequate, only for him to learn to his sorrow later, when he applies for admission to the examinations for certification in gastroenterology, that the Subspecialty Board does not approve of his supposedly mature selection and finds him ineligible for the examination?

Some short-sighted and narrow-minded internists who have always been hostile to subspecialties in medicine, have interpreted the new regulations to mean that the American Board of Internal Medicine desires to eliminate training programs and residencies in gastroenterology. They have seized upon some of the ambiguous phraseology of the directives to justify their interpretation. I must confess that the language of the statements made is sometimes difficult

to understand. Witness, for example, the following exchange of telegrams between a hospital and the Council on Medical Education and Hospitals:

Hospital to Council:—"In view of your letter of 3 October will you answer this question. Can a hospital have an approved residency with a resident in gastroenterology after 1 July 1961?"

Council to Hospital:—"Approval of residencies in gastroenterology will cease as of 1 July 1961. If resident remains at hospital he should contact American Board of Internal Medicine concerning credit."

I have discussed this problem with a number of physicians who have for many years conducted approved residency training programs in gastroenterology. Although a rather intensive training program has been established by all of us for the resident in gastroenterology, our staffs are integral parts of the departments of medicine and we actively participate in the teaching of this specialty to the interns and residents in internal medicine. All of us feel that a program of subspecialty training in gastroenterology must be based upon a broad knowledge of the general field of internal medicine. We agree with the recommendation of the committee of the American Gastroenterological Association that an optimal foundation for graduate training in gastroenterology would include, beyond a one year internship, two years of residency in general internal medicine.

The Committee on Education and Training, in their report previously mentioned states that any good and comprehensive training program will almost certainly contain the ingredients requisite for eventual certification by the Subspecialty Board in Gastroenterology. We all agree. We should therefore urge the American Board of Internal Medicine to rescind its new policy. If this is not done then our own regulating body should continue to approve training programs, and list such approved programs in appropriate directories and journals of gastroenterology, for the guidance of applicants for Residencies or Fellowships in Gastroenterology.

REFERENCES

1. On Specialization and Gastroenterology—Chairman's address, Section on Gastroenterology and Proctology, the 109th Annual Meeting of the American Medical Association, Miami Beach, 15 June 1960. *J.A.M.A.* **174**:1606-1610, (19 Nov.), 1960.
2. Post Graduate Training in Gastroenterology. *Gastroenterology* **39**:262-269 (Aug.), 1960.
3. Special Announcements and Notices. *J.A.M.A.* **174**:817-818 (8 Oct.), 1960.

ISIDORE A. FEDER, M.D., F.A.C.P., F.A.C.G.

President's Message

REGIONAL MEETINGS

It is not always possible for all of the membership to attend each Annual session of the College and so the idea of holding Regional Meetings in various parts of the country was initiated. After a lapse of three years, we will again have Regional Meetings in Continental United States, so that more of our members will have the opportunity of attending sessions, meeting their colleagues, augmenting their medical knowledge and, in general, participating more actively in the programs of the College.

Last month, in my message, I announced that we hoped to have four Regional Meetings during 1961. I am most gratified by the enthusiastic reception this plan was accorded on the part of the Governors and those others in the areas in which these meetings were to be held. We now have preliminary plans started for the following meetings:

Western Regional Meeting—San Francisco, Calif., Sunday, 5 March 1961.

Southern Regional Meeting—Houston, Texas, Sunday, 19 March 1961.

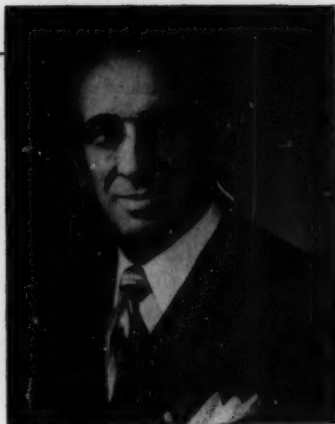
Central Regional Meeting—Milwaukee, Wisc., Sunday, 16 April 1961.

Eastern Regional Meeting—New York, N. Y., date to be announced.

Detailed information concerning the program, time and exact place of each meeting, will be sent to the membership in the various sections of the country. If you wish to present a paper on the program of one of these meetings, contact the Governor for your state or district or, write directly to the Executive Director at the Headquarters Office.

Whether you are on the program or not, plan to attend the Regional Meeting in your area. I am confident that you will gain much by doing so.

Henry Baker



ABSTRACTS FOR GASTROENTEROLOGISTS

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ESOPHAGUS

ESOPHAGITIS: Michael W. Shutkin. *Wisconsin M. J.* 58:219 (Apr.), 1959.

Dr. Shutkin divides esophagitis into 3 main varieties: 1. Acute esophagitis. The etiologic factors are chemical, thermal, mechanical and infectious agents. The symptoms may include severe substernal pain radiating to the neck, arms or scapulae with dysphagia. In the corrosive poison type, eventually the formation of an elongated stricture is characteristic. 2. Subacute recurrent esophagitis. This type is sometimes more specifically called peptic reflux esophagitis. The etiologic factors are intubation, surgical procedures on the esophagus, vomiting (especially if associated with duodenal

ulcer), and sliding hiatus hernia. 3. Chronic esophagitis. In this group are included entities entitled esophagogastric and marginal ulceration, with short esophagus. The etiologic factors are congenital short esophagus, operations upon the esophagus and cardiospasm. In types 2 and 3 (subacute and chronic esophagitis), reflux of gastric juice, peptic reflux is believed to be the etiologic factor although there are some factors against this. For example, achlorhydria is sometimes present.

SAMUEL L. IMMERMANN

BLEEDING ESOPHAGEAL VARICES: Robert J. Freeark, John Tobin, Jr. and Donald D. Kozoll. *Illinois M. J.* 116:150 (Sept.), 1959.

This is a seminar of bleeding from esophageal varices developed at Cook County Hospital. It is primarily a discussion of the use of the Sengstaken-Blakemore tube in the control of hemorrhage.

In the series of cases under discussion, this tube was used in 30 patients. Five of these patients were found to have bleeding ulcer rather than varices and were excluded therefore from the remainder of the discussion. Fifteen of the 25 cases of bleeding varices died within 96 hours of the onset.

Of the remaining ten, four died within 30 days. Of the remaining six, three had successful portacaval shunts and three refused surgery and were lost to follow-up.

The authors give a very detailed plan for the use of this tube and point out that it is strictly an emergency treatment and not definitive therapy but can be a life saver in a few incidences and allow the purchase of time in which to prepare the patient for more definitive therapy.

PAUL LEDBETTER

STOMACH

DUODENAL ULCER: THE PRESENT STATUS OF DEFINITIVE SURGERY: THE SELECTION AND MANAGEMENT OF PATIENTS UNDERGOING OPERATION: John R. Brooks and Francis D. Moore. New England J. Med. 260:1069 (21 May), 1959.

This is part of a continued series under Medical Progress. The discussion is concise, thorough, and defines patients according to their needs for definitive surgery and their prospects for good results. Patients not requiring definitive ulcer surgery are discussed as to age, sex, symptoms, and clinical situations. Patients requiring definitive surgery with expectancy of good results are discussed as to build, age, secretory potentials, obstructive symptoms, bleeding, perforation, and technical difficulty. The prin-

ciples of management of massive hemorrhage are outlined.

Patients requiring surgery, but not tolerating it well, and patients with previous surgery, with recurrence or complications are discussed. The association of ulcer with endocrine disturbances is noted. The values of acid and pepsin secretion in various situations is discussed. The article is to be concluded in a future issue.

BERNARD FARFEL

DUODENAL ULCER: THE PRESENT STATUS OF DEFINITIVE SURGERY; THE SELECTION AND MANAGEMENT OF PATIENTS UNDERGOING OPERATION: John R. Brooks and Francis D. Moore. New England J. Med. 260:1124 (28 May), 1959.

The authors suggest in the uncomplicated case that early postoperative management would not include such things as antibiotics, blood transfusions, and would utilize nasogastric suction during the first night postoperatively, the tube being removed the following morning. It is considered by them in good taste to use catheter gastrostomy for suction in patients who do not tolerate nasopharyngeal intubation without undue distress. So far as diet and maintenance of weight are concerned, they anticipate some loss in weight for several days following operation and postoperative fluid-electrolyte care is given to suit the need in each individual case. They see no necessity in abolishing the normal catabolic losses by the use of high intravenous intake in the immediate postoperative period. They do, however, give special attention to any patient in whom there is any broncho-pulmonary drainage for the swallowing of any toxic or infectious substances may be deleterious to the postoperative result.

Peritonitis which was formerly one of the common causes of death after subtotal gastrectomy remains one of the immediate postoperative hazards. In almost all instances death is due to a duodenal leak which has as its basis insufficient circulation in the operated duodenum. It may

likewise stem from excessive dissection around an inflamed area or the unnecessary compulsion to dissect out the ulcer and remove it. To anticipate or foresee the possibility of a poorly vascularized duodenal closure is to prevent this complication. Should the surgeon find himself at the point of no return and is unable to close the duodenal stump, intubation of the stump must be employed. It is felt that the duodenal stump presents the greatest problem in the acute bleeder. Once duodenal leakage has been recognized, if it occurs, the treatment is to at once institute some drainage to minimize enzymatic skin digestion, and fortunately most of the duodenal fistulas after a Billroth II gastrectomy will close spontaneously and alimentation may proceed concurrently. Major re-operation is rarely needed. The challenge in these cases is to manage the electrolyte losses adequately. In this instance, antibiotics are given freely in very large doses with penicillin and streptomycin being the drugs of choice initially.

In cases of postoperative pancreatitis which usually results from excessive dissection around the pancreas or accidental ligation of the duct of Santorini management is conservative with antibiotics, fluids, colloids, and parasympathetic blocking agents. Gastric intubation is a vital part of the

treatment and minimizes the secretory effect on the pancreas produced by hydrochloric acid. If jaundice exists, cholecystostomy is indicated.

In the not too rarely occurring stomal delayed cases, one may be forced to employ a jejunostomy for the restoration of nasogastric tube losses and for feeding until opening of the stomach occurs. It is pointed out that if vagotomy has been done the likelihood of this complication is greatly increased. It is suggested that in the

late postoperative management, frequent small feedings and avoidance of foods which bother the patient are usually sufficient to relieve the so-called dumping syndrome which is not always due to the same causes. Certainly it is not more common in any of the various modifications of the Billroth I or II operations frequently employed. Loss of weight in the patient after gastrectomy is probably most frequently due to inadequate intake.

L. K. BEASLEY

CHRONIC MYELOGENOUS LEUKEMIA WITH GASTRIC INFILTRATION: John A. Cavina, Hugh S. Levin and H. James Day. *New England J. Med.* 260:1111 (28 May), 1959.

This article reports a case of chronic myelogenous leukemia with gastric infiltration in which the presenting symptoms were those of disease limited to the gastrointestinal tract. The patient reported a feeling of fullness in the epigastrium after meals which after several weeks changed to a frank burning epigastric discomfort.

At operation the lesion appeared grossly to be a carcinoma of the stomach and it was not until microscopic sections were studied that the true nature of the tumor became apparent.

This case has been reported because of

the extreme rarity of its occurrence. A comprehensive review of the statistical data at present available would suggest that infiltration of the stomach due to myelogenous leukemia occurs about 10 per cent as frequently as does infiltration in cases suffering with lymphosarcoma, reticulum-cell sarcoma, or lymphatic leukemia.

The most important thing about reporting this single case is that surgical intervention made possible the removal of the chief complaints of the patient.

L. K. BEASLEY

HIATAL HERNIA, REFLUX ESOPHAGITIS, AND THE ULCER DIATHESIS: Herbert R. Hawthorne. *Pennsylvania M. J.* 62:695 (May), 1959.

Hawthorne discusses reflux esophagitis, chiefly from the standpoint of surgical treatment.

If the diagnosis has been made by symptoms, x-ray examination and esophagoscopy, the treatment may be either medical or surgical. The time for surgical treatment depends on the bias of the surgeon. If there is no response to medical treatment, and deep ulceration, fibrosis and marked stenosis are present, surgical treatment is indicated. Medical treatment of a duodenal ulcer and dilatation of a not-too-far advanced stricture is often successful. Some surgeons feel that a hernia of fair size should be repaired even if there is no esophagitis. If there is a hernia, the thoracic approach is the most satisfactory; if a duodenal ulcer is present, the abdominal approach is better. In the type of esopha-

gitis in which neither hernia nor duodenal ulcer are present, a standard subtotal gastrectomy is advocated to eliminate the acid peptic factor. In some cases, after this operation, a few dilatations will relieve a stricture. Hawthorne discusses other types of surgical treatment. In advanced stages of esophagitis, resection of the lower part of the esophagus is required, although this has the disadvantage of possibly destroying the protection of the esophagogastric junction. Various types of operation can be performed. Hawthorne prefers esophagogastric anastomosis with pyloroplasty; he states that it is apparent that surgeons are still searching for better methods of dealing with this difficult problem. In a hiatal hernia in a poor risk patient, only an occasional good result follows phrenicectomy.

SAMUEL L. IMMERMAN

THE EVALUATION OF EMERGENCY GASTRECTOMY FOR HEMORRHAGE FROM THE UPPER GASTROINTESTINAL TRACT: J. R. Bingham. *Canad. M.A.J.* 80:704 (1 May), 1959.

The author considered that a patient under 45 years of age with massive hemorrhage or of any age with hemorrhage insufficient to produce shock was in essence a good risk patient and was treated conservatively.

Patients over the age of 45 years with massive hemorrhage were considered poor risk patients and were treated conservatively unless the bleeding either: a) did not stop within 48 hours or, b) recurred after once stopping. In either of the latter events emergency gastrectomy was carried out.

The author feels that in the absence of

demonstrable lesions on no touch roentgenograms, emergency gastrectomy is not indicated. He points to the fact that in his series 139 patients were in this group and none of these conservatively treated patients died of hemorrhage.

Death rate was reduced from 11.7 per cent for the patients treated conservatively to 4.7 per cent for the patients treated both conservatively and by emergency gastrectomy in patients selected according to this criteria. Six hundred and ninety-two patients bleeding from benign peptic ulcer comprised this study.

GLENN S. ROST

PROLONGED TREATMENT OF PEPTIC ULCER WITH HOMATROPINE METHYLBROMIDE: A STUDY OF 58 PATIENTS UNDER CONTINUOUS THERAPY FOR PERIODS UP TO ONE YEAR: C. James Walton, David Cayer and M. Frank Sohmer. *North Carolina M. J.* 20:181 (May), 1959.

Fifty-eight patients with chronic recurring peptic ulcers were treated for periods varying from 1-12 months with homatropine methylbromide (Malcotran) repeat action tablets. A six-feeding bland diet and antacids were also given.

During the period of therapy 25.9 per cent of patients were asymptomatic and an

equal number were unchanged or worse. In 74.1 per cent the results were classified clinically as fair to excellent.

The incidence of side-effects was comparatively low, only five patients having to discontinue medication because of unpleasant reactions.

THEODORE COHEN

PARTIAL GASTRECTOMY AND PEPTIC ULCER: Hermon Taylor. *Brit. M. J.* 5130:1133 (2 May), 1959.

The surgical technic void is clearly described in the text and illustrated by diagrammatic drawings. It briefly consists in mobilization of a tube formed from the gastric fundus which is anastomosed to the jejunum at the ligament of Treitz after minimum 75 per cent resection of the stomach. The disadvantages inherent in both retrocolic and antecolic anastomoses are avoided by elimination of the afferent jejunal loop. It also avoids the obstructing kink apt to occur at the upper end of the anastomosis, which by necessity is placed

at least 3 inches superior to the origin of the jejunum. In the antecolic anastomosis two serious effects are avoided by eliminating the adhesions apt to occur in coils of efferent jejunum in the region of the spleen and by avoiding the possibility of obstruction by creating a gastrojejunal sling in front of the other viscera.

The original article is highly recommended for clarity and presentation of a method of gastric resection for avoiding postoperative complications.

JOSEPH E. WALTHER

IMMEDIATE POSTOPERATIVE COMPLICATIONS OF PARTIAL GASTRECTOMY: J. C. Grant. *J. Internat. Coll. Surgeons* 31:529 (May), 1959.

An analytical attempt to lower a 2.1 per cent mortality in 240 consecutive partial

gastrectomies done for peptic ulcer is made by this author.

Hemorrhage, anastomosis leakage, pulmonary complications including tuberculous bronchopneumonia, vasovagal response, and intestinal obstruction were the most serious complications.

A narrative analysis of each complication is presented and a plea for early recognition of them is made.

Faulty suture technic and ischemic necro-

sis at the suture line are assigned as some of the causes of leakage.

Pulmonary tuberculosis was noted in 4.2 per cent as a postoperative complication.

One death followed atropine and prostigmine administration and another resulted from intestinal obstruction in a patient with a reversed rotation of the intestine.

GLENN S. ROST

PEPTIC ULCER—A CHEMICAL IMBALANCE: Ejnar Jarlov, Erik Friis, Jacob M. Leavitt, Charles R. Dugan, Vojislav I. Mitrovic, Norman A. Samuels and Joseph H. Tuchman. *Am. J. Proct.* 10:198 (June), 1959.

This is a report of the use of the nutritional wafer 'Exul' in the treatment of peptic ulcer. Exul is a combination of fat-soluble and water-soluble extracts of calf's brain, together with dried milk solids, iron and Vitamin B-complex. The authors believe that peptic ulcer results from a specific nutritional deficiency, and that Exul remedies this deficiency because it contains an ulcer-protective factor. Exul was used in the treatment of 141 cases of peptic ulcer without any other medication and

without restrictions of diet, alcohol or tobacco. Those cases responding to Exul usually had immediate and complete symptomatic relief, while those cases not responding were failures from the start. The authors conclude that the nutritional wafer 'Exul' is as good as conventional therapy in 80 per cent of cases, and that it provides a needed dietary factor in cases of peptic ulcer.

ARNOLD STANTON

INTESTINES

CARCINOMA OF COLON AND RECTUM: Robert O. Gregg, Bruce E. Chamberlain and Arthur A. Vercillo. *J.A.M.A.* 170:143 (9 May), 1959.

In a review of results obtained in the treatment of 623 patients with carcinoma of the colon the authors report the following observations:

There was a lower incidence of anemia than is usually reported.

Carcinoma arising below the peritoneal reflection is very low.

Age of patient is a most important factor in five-year survival. Younger people have a greater number of five-year cures.

Acute obstruction is the most common complication of cancer most likely to end fatally. There was a 22 per cent mortality among patients admitted with this complication, while only 3.7 per cent operative mortality in patients who underwent

planned surgery.

Peritonitis developed in 8 per cent of cases in spite of antibiotic treatment.

Anterior resection is procedure of choice for lesions arising from 10 to 15 cm. from the anal verge.

There is relatively little difference in survival rate according to the site except that a poor prognosis is evident for patients in whom there is involvement of the extraperitoneal portion of the rectum.

Local fixation of a lesion to a locally resectable site and extension to the serosa is not necessarily a bad prognostic sign.

Nodal involvement is of no significance except in rectal cancer.

A. J. BRENNER

POSTVAGOTOMY DIARRHEA: ITS CAUSE AND PREVENTION: Harold Burge and Peter A. Clark. *Brit. M. J.* 5130:1142 (2 May), 1959.

A review of many different series of patients who have undergone vagotomy demonstrate almost uniform incidents of post-

operative diarrhea in 30 per cent. Most authors have believed the diarrhea to result from infection consequent upon gastric

hypocidity or to gastric stasis.

Twenty-five consecutive patients were given selective vagotomy in which the anterior vagus was divided, leaving the posterior vagus intact. There was no occurrence of bowel abnormality in these patients compared to 40 per cent of patients who devel-

oped diarrhea in which no attempt was made to preserve the coeliac division of the posterior vagus. The evidence was considered conclusive that diarrhea is caused by denervation of the coeliac plexus when the posterior vagus nerve is divided.

JOSEPH E. WALTHER

THE MALABSORPTION SYNDROME AND DIARRHEA: A PANEL DISCUSSION:

INTRODUCTION: David J. Sandweiss; PATHOGENESIS OF PRIMARY MALABSORPTION SYNDROME: David Adlersberg; ABSORPTION TESTS IN THE DIAGNOSIS OF INTESTINAL MALABSORPTION: Arthur B. French; THE ROENTGEN FINDINGS IN THE MALABSORPTION SYNDROME: Richard H. Marshak; PRIMARY MALABSORPTION: Henry L. Bockus; THERAPY OF PRIMARY MALABSORPTION: Robert J. Priest; QUESTIONS AND ANSWERS IN DISCUSSION: SUMMARY OF PANEL: David J. Sandweiss. J. Michigan M. Soc. 58:772-792 (May), 1959.

This panel discussion deals with primary malabsorption, celiac disease, nontropical sprue, and sprue. Secondary malabsorption is due to disease entities affecting the small bowel.

This syndrome is a genetically transmitted metabolic disorder of malabsorption and hematologic abnormalities. Symptoms are diarrhea, weight loss, glossitis, distention, hemorrhagic manifestations, tetany, and paresthesias. Diagnosis is based on steatorrhea, anemia, flat glucose and Vitamin A tolerance tests, hypochlosteremia, hypocalcemia, and the typical "sprue-pattern" of small bowel on x-ray examination.

The roentgen findings of dilatation, segmentation, hypersecretion, motility changes, and alterations of mucosal markings are all included under the term "deficiency pattern". When marked, they are diagnostic of certain malabsorption states, sprue, lymphosarcoma, and Whipple's disease. In sprue, dilatation is marked and may affect the colon as well. In spite of this, the *calculae conniventes* are quite prominent. Segmentation is also marked, usually in the ileum, and is associated with fragmentation or scattering of the barium. Hypersecretion is

constant and causes air fluid levels. Pancreatic steatorrhea is associated with a normal bowel, so that these findings tend to rule out this condition.

Until World War II treatment was empiric. It was then found that exclusion of gluten in flour led to favorable results. The diet should include high protein, low fat, and high vitamin content, with simple sugars rather than starches. Supplemental Vitamins A, D, and K orally, and B-complex parenterally is useful. For the anemia, folic acid, B₁₂, crude liver extract, and parenteral iron are indicated. Calcium and potassium must be replaced. When diet, vitamins, minerals, and drugs fail, steroids may give prompt improvement. Particularly in the acute case, oral or parenteral steroid may be used, decreasing the dosage to maintenance levels as progress is shown. Spontaneous remissions are not infrequent, so that the effects of drugs are difficult to evaluate. The goal of treatment is to improve nutrition and correct the deficiency states and allay nervous stress.

An excellent summary of the panel concludes the presentation, touching all the highlights of the question period as well.

NORMAN L. FREUND

FECAL IMPACTION IN MODERN PRACTICE: Karl-Albert Dresen and Guy L. Kratzer. J.A.M.A. 170:644 (6 June), 1959.

Organic causes include obstructing lesions, anal fissure, and diseases such as megacolon, general paresis, and infantile paralysis. Fecal impaction occurs at any age and can mimic other diseases by producing symptoms suggesting diarrhea, tu-

mor, or urinary calculi. Physical examination may reveal a hard fecal mass in the rectum, a hard, putty-like mass at the end of the sigmoidoscope, distended abdomen, or palpable hard lumps in the abdomen. Impacted scybala in the lower part of the

sigmoid may be dislodged by pelvic, abdominal, or sigmoidoscopic manipulation.

Treatment is easy after the diagnosis is made. Impactions in the rectum can be broken or dislodged with the finger. Plain water enemas are helpful. Use of hydrogen peroxide has been discontinued because of the frequent sequela of proctitis. The patient should be in the knee-chest position, as water will not run uphill. Mineral oil instillations and enemas are used when the impaction is in the sigmoid or higher. The use of castor oil or similar laxatives by mouth in the presence of rock-like impacted stool in the rectum and colon is contraindicated because of the danger of precipitating complete obstruction, rupture of a diverticulum, or anorectal trauma. One must remember that in fecal impaction the

intestine is partially obstructed and dilated. It is best to decompress it by means of enemas and continue this decompression for a number of days or until the intestine has regained its normal tone, after which an anticonstipation regimen with peristaltic stimulants may be used.

Fecal impactions in the lower part of the sigmoid may be dislodged by pelvic, abdominal, or sigmoidoscopic manipulation. For suspected impaction higher in the colon the colonic irrigation is a pertinent form of therapy. For organic strictures beyond the reach of the sigmoidoscope, surgical decompression is frequently necessary. However, colonic irrigations with the patient in the knee-chest position should be given a fair trial.

ALVIN D. YASUNA

THE TREATMENT OF ULCERATIVE COLITIS: E. S. R. Hughes. New Zealand M. J. 58:287 (June), 1959.

Most progress in the treatment of ulcerative colitis has been made surgically so that there is a trend to treat more cases by operation. In this review a personal series of 176 cases of ulcerative colitis is analyzed.

In most patients symptomatic relief is best obtained with a low residue diet. It does not seem necessary to give steroid therapy, and psychotherapy is not indicated.

Chronic ulcerative colitis should be treated by surgery. Surgical management has improved, and with one operation it is possible to remove the entire large bowel

and construct an ileostomy that is easy to manage. Despite the fact that the rectum appears in many cases to be relatively mildly involved, the author was not fortunate with ileorectal anastomosis. The incidence of cancer is very high in patients with chronic ulcerative colitis of 10 years' or more duration.

Acute ulcerative colitis is serious. Although the occasional patient will survive with general supportive measures, the risk of surgery appears less.

JACOB A. ROESE

POLYPS OF THE COLON AND RECTUM: J. Alfred Rider, Joseph B. Kirsner, Hugo C. Moeller and Walter L. Palmer. J.A.M.A. 170:633 (6 June), 1959.

In a six-year period, 9,669 proctosigmoidoscopic and x-ray examinations resulted in detection of polyps in 537 patients.

Of the 537 patients 372 had follow-up examinations four or more years after their original polyps were discovered. The rate of formation of new polyps of the colon in this group was very high, 153 patients or 41.1 per cent. The incidence of carcinoma of the colon in 9,132 patients without polyps was approximately 2 per cent. Among the 537 patients with polyps, the incidence of carcinoma in the polyps was 5.8 per cent. Local treatment, i.e., removal by biopsy or snare, with fulguration of the

base, appears to be adequate in dealing with the histologically benign polyp within reach of the proctosigmoidoscope. Large polyps in the rectum or colon should be removed surgically. Polyps with focal areas of carcinoma, but without invasion of the stalk (adenocarcinoma grade 1 and carcinoma *in situ*), may be treated in the same manner as benign polyps, with frequent re-examination of the rectum and colon by proctosigmoidoscopy and barium enema. If invasion of malignant cells is demonstrated in the stalk of a pedunculated polyp or in the intestinal wall, the preferred treatment is that required for carcinoma.

The presence of a polyp in the colon or rectum is an indication of an abnormal mucosa prone to develop new polyps, benign or malignant. New polyps developed in approximately 40 per cent of patients with polyps of the colon and rectum observed for from four to nine years. The yearly new polyp formation rate, approximating 10 per cent, indicated a group of patients prone to develop polyps and requiring frequent reexamination.

The incidence of carcinoma of the colon was twice as high in patients with multiple

polyps as in those with single polyps; the lowered incidence of subsequent carcinoma of the colon suggests the beneficial effects of early diagnosis and removal of polyps. Local removal appeared to be adequate treatment for benign polyps and for adenocarcinoma within reach of the proctosigmoidoscope. Patients with polyps should be examined annually until findings of at least five consecutive yearly proctosigmoidoscopic and roentgenologic examinations of the rectum and colon have been negative.

ALVIN D. YASUNA

THE DIAGNOSIS OF CANCER OF THE COLON: E. G. Muir. *Central African J. Med.* 5:306 (June), 1959.

The author notes that the average duration of symptoms in carcinoma of the colon before diagnosis and admission to the hospital was five to six months. While the most important factor in prognosis is the biology of the growth, early diagnosis and prompt treatment are still of the utmost significance. To achieve this the author makes a plea for more detailed and complete histories in the patients' own words.

The relative frequency of the complaints were studied in a series of 714 cases to delineate a common pattern, if possible. Abdominal pain, flatulence or discomfort were the most frequent, 68.9 to 78 per cent. Alteration in bowel habit was also important, ranging from 30 per cent in the

right colon to 70.1 per cent in the sigmoid. Vomiting was present in about 3.5 to 32 per cent depending on the location of the lesion. Weight loss, bleeding, faintness, passage of mucus and the presence of a mass were variable but usually late symptoms.

Differential diagnosis includes the consideration of peptic ulcer, appendicitis, diverticulitis, ulcerative colitis and hemorrhoids. Although investigation in a patient suspected of cancer proves to be negative, one should not be lulled into a sense of false security. The case should not be dismissed but should be kept under constant review, for repeated investigations occasionally produce the positive result.

LOUIS A. ROSENBLUM

AGANGLIONIC MEGACOLON IN THE FIRST YEAR OF LIFE: Felix A. McParland, Bernard J. Spencer and Tague C. Chisholm. *J. Lancet* 79:284 (June), 1959.

The treatment of the newborn child who has intestinal obstruction due to a segment of aganglionic colon is discussed. Symptoms of this condition are manifested soon after birth, and should be thoroughly investigated promptly. A flat film of the abdomen shows partial obstruction in these cases. A large bowel study should then be done with a thin barium mixture or a trickle of Radiografin. In megacolon cases, only a small amount should be used, since larger amounts are difficult to remove, and may obscure the transitional zone, which is the diagnostic feature of the disease. It is also preferable not to cleanse the colon before the contrast study. Since changes in the caliber of the colon are of such short dura-

tion that with adequate cleansing, the colon may appear normal on examination. Another important point is the way in which the catheter is inserted, which should be just across the anorectal threshold. If it is inserted too far, a short aganglionic segment may be overlooked. If there is still doubt after the low colon study, a rectal wall biopsy will establish the diagnosis.

The authors recommend a transverse colostomy be done as soon as the diagnosis is established. The children usually do well, and a definitive pull-through procedure can then be done with safety between 18 and 24 months of age.

SAMUEL M. GILBERT

PNEUMATOSIS CYSTOIDES INTESTINORUM HOMINIS: Jacob Reichert. *Am. J. Proct.* 10:181 (June), 1959.

Pneumatosis intestinalis is characterized by the formation of innumerable blebs under the visceral serosa of the intestinal tract. The blisters vary in size and shape and are filled with gas. This condition is frequently accompanied by free air under the diaphragm, ascites and malnutrition. Intestinal obstruction, intussusception and volvulus may complicate the original condition.

A case of intestinal pneumatosis is described in a 65-year old woman, who was operated on for intestinal obstruction. Flat plate of the abdomen showed a massive amount of free air under the diaphragm,

with fluid levels in the small bowel. After correcting dehydration and electrolyte imbalance, exploration revealed an obstruction in the ileum due to a granulomatous area. The small intestine was covered with innumerable gas cysts varying in size from a pinhead to a pea. Volvulus of the jejunum resulted in intestinal obstruction six weeks postoperatively, at which time exploration revealed the complete absence of gas cysts in the intestinal tract. The patient expired and autopsy disclosed multiple adhesions of the peritoneum, pleura, pericardium and stomach.

ARNOLD STANTON

ACUTE BACILLARY DYSENTERY IN CYPRUS: P. J. Taylor. *Brit. M. J.* 5139:9 (4 July), 1959.

This is a study of comparative treatment of 332 cases of acute bacillary dysentery in Cyprus.

All cases were admitted to hospital; the diagnosis was made on clinical evidence as well as isolation of a shigella (Flexner or Sonne).

This was a controlled study. Some patients were given specific treatment, while others were given only supportive treatment. (Vitamins, Kaolin, etc.)

The results were measured in clinical improvement and negative bacteriological

report on six successive days.

A full course of insoluble sulfonamides consisted of 125 gm. in six days. A full course of phthalylsulfathiazole was much more effective in cure of acute bacillary dysentery—both clinically and bacteriologically than supportive treatment alone.

A mixture of soluble sulfonamide and streptomycin in moderate dosage gave better results than full course of insoluble sulfathiazole alone and was much more acceptable to the patient.

LIONEL MARKS

SULFONAMIDES AND STREPTOMYCIN IN BACILLARY DYSENTERY: J. Fališevac, Z. Kosutic and M. Galinovic-Weisglass. *Brit. M. J.* 5139:12 (4 July), 1959.

A controlled group of patients in Zagreb with acute bacillary dysentery was treated with sulfonamides, sulfonamides with streptomycin and streptomycin alone.

Bacillary dysentery due to *Sh. flexneri* was quickly cured both clinically and bacteriologically by the sulfonamides.

Bacillary dysentery due to *Sh. sonnei* responded more satisfactorily and quicker to

a combination of sulfonamides and streptomycin.

The response to streptomycin alone in either group was not satisfactory. The response to symptomatic treatment alone in either group was poor both clinically and bacteriologically.

LIONEL MARKS

INTESTINAL DIVERTICULA: John K. McCollum. *Brit. M. J.* 5140:34 (11 July), 1959.

Diverticulosis is a disease of the entire gut although the occurrence of a complication may direct the attention to a particular segment. Most diverticula of the intestinal tract are protrusions of the mucous and submucous layers through the muscular

coat (Pulsion diverticula). Diverticula may be found in all four parts of the duodenum. All cases studied complained of dyspepsia not unlike that of cholecystitis or chronic peptic ulcer. Although it was formerly taught that duodenal and ileocecal diver-

ticular were to be disregarded as causes for dyspepsia, it is suggested that the reverse may be true since a concomitant diverticulum may be responsible for the major disability in patients with chronic duodenal ulcer or biliary disease. Rarely, however, are the symptoms severe enough to require surgical resection of duodenal diverticula.

Jejunoileal diverticula are less common, usually cause hematemesis and melena and often require surgical resection.

Of 90 cases of colonic diverticula studied

60 presented recurrent attacks of abdominal pain, diarrhea or signs of peritonitis. Diverticula in any part of the colon may develop complication such as diverticulitis, hemorrhage (moderate to severe), perforation with peritonitis, pericolitis with obstruction, abscess, and fistula formation. The presence of a chronic diverticulum is not an invitation to surgery. Their complication, however, may require surgical intervention.

A. J. BRENNER

HIDDEN LESIONS OF THE SIGMOID COLON: Marvin E. Sattler and Robert W. Mann. *Wisconsin M. J.* 58:361 (July), 1959.

Lesions of the sigmoid colon are frequently obscured through anatomical peculiarities of this segment of the bowel. The most painstaking x-ray examinations will miss the lesions in 5 to 10 per cent of colons thus examined. The sigmoidoscope also fails to visualize lesions in certain multicoiled sigmoids. This is not to be construed as criticism of the roentgenologist or examining proctologist because the redundant and often coiled sigmoid colon will obscure some areas even if all possible diagnostic means are used. In doubtful cases, the radiologist uses the lateral, oblique, angle oblique, angle anteroposterior, and the Chassard-Lapine positions to demonstrate hidden lesions of the sigmoid colon.

Two cases were presented as extreme examples of prolonged observation in patients who have blood in the stool. The

authors have reason to believe, however, that this is not an uncommon practice and that treatment is frequently delayed in a patient who might be favorably treated in the early stages of the disease. Exploratory laparotomy should not be considered so hazardous a procedure as to await absolute diagnosis in these instances. There is reluctance by both internist and surgeon frequently to attack these diagnostic problems surgically. The patient who has blood on the stool and has had a thorough work-up including sigmoidoscopic and x-ray examination with barium enema without finding a source of bleeding, should be considered a candidate for exploratory laparotomy, after a short period of observation and having had the diagnostic studies repeated.

ALVIN D. YASUNA

MECHANICAL INTESTINAL OBSTRUCTION AND ILEUS: USE OF PROCAINE HYDROCHLORIDE IN DIFFERENTIAL DIAGNOSIS AND AS A THERAPEUTIC AGENT: Leon A. Frankel. *J. Internat. Coll. Surgeons* 32:135 (Aug.), 1959.

An injection of a few c.c. of 1 per cent sterile procaine hydrochloride was introduced into the abdomen to attempt peristaltic stimulation of a questionable viable segment of the small intestine. Its significance became apparent when it was used several times subsequently for the same purpose. The procaine hydrochloride can be introduced into the gastrointestinal tract by an indwelling tube, by fistulization (cecostomy), or through an abdominal catheter into the peritoneal cavity.

It appears this agent directly affects the postganglionic fibers of the parasympathetic nervous system which arise from the cells

situated in or in close proximity to the innervated organ, resulting in increased tone and motility of both the small and the large intestine.

The procedure can be used as a diagnostic sign for: 1. In differentiating between intestinal obstruction and ileus. 2. Clinically there is a positive or negative effect on the extrinsic or intrinsic nerve supply of the intestine and upon the myogenic tonus, depending on the viability of the bowel from either nutritional or mechanical point. 3. Injected immediately after operation on the gastrointestinal tract to initiate early intestinal motility. 4. Intestinal motility can

be determined early, obviating need of operation for ileus or obstruction. 5. Post-operative alimentation can be established much earlier.

The author then cites about 60 cases so treated with fairly good results.

LOUIS K. MORGANSTEIN

DIAGNOSIS AND MEDICAL TREATMENT OF AMEBIASIS: Frank C. Golding and Gordon L. Black. *Texas J. Med.* 55:688 (Aug.), 1959.

The authors stressed the importance of prolonged treatment regardless of which drugs are used. They do not feel that the broad spectrum antibiotics should be used at all unless the patient is unable to tolerate arsenic or iodine preparations, or when the disease is complicated by other infections in which these drugs are specific. The one exception to this objection is Fumagillin. This antibiotic has little use except in the treatment of amebiasis. At present, the authors give continuous treatment for 15 weeks or more, followed by equal amounts

of medication on interrupted schedule with one or two weeks rest between each change of medication. They further recommend 3 to 5 weeks treatment each six months for two years, then once yearly thereafter.

The authors present two cases to demonstrate the need for longer treatment and follow-up than has been considered necessary previously. They also feel that all so-called nonpathogenic ameba should be eradicated as they apparently are pathogenic in some cases.

PAUL LEDBETTER

TECHNIC AND INDICATIONS FOR MILLER-ABBOTT TUBE INTUBATION: A RAPID METHOD OF INTRODUCTION: Ralph H. Loe and C. E. M. Touhy. *Am. J. Surg.* 98:160 (Aug.), 1959.

The Miller-Abbott tube as introduced in 1938 marked an important milestone in the management of intestinal obstruction. The mortality rate for this condition prior to the introduction of intubation was 29.6 per cent, and was reduced to 5.9 per cent after its use. Many tubes were developed, but successful introduction was difficult and often required 24 hours. While the use of these tubes was considered a valuable adjunct in the management of small bowel obstruction, the difficulties of introduction resulted in many surgeons abandoning their use.

The authors prefer to pass the tube in the patient's room, and a list of equipment needed is given. Ten steps for the introduction of the tube are outlined. Every detail should be followed in order to make possible the quick and successful introduction of the tube through the pylorus

into the second portion of the duodenum. The patient is then taken to the fluoroscopy room and the tube, having passed the pylorus, is easily advanced to the lower third of the second part of the duodenum. The stylet is then pulled out, after an injection of 10 c.c. of mineral oil. With the patient back in his room, intermittent suction is applied and the tube is advanced at the rate of about 6 inches an hour. Roentgen films should be taken periodically to determine the progress of the tube. When x-ray films indicate complete deflation of the small bowel, the air is removed from the bag and suction is discontinued. If withdrawal of the tube is indicated, it should be done gradually so as not to intussuscept the bowel.

Principal uses for the Miller-Abbott tube intubation are enumerated.

CARL J. DePRIZIO

LIVER AND BILIARY TRACT

INDICATIONS OF VITAMIN K₁ IN LIVER PATHOLOGY: P. Kissel, G. Rauber, G. Debry, M. Laxenaire and F. Cherrier. *Semaine des Hopitaux de Paris* 35:938 (March), 1959.

The action of Vitamin K₁ upon the clinical course and upon prothrombinemia is

studied in patients suffering from various liver diseases.

After briefly stating their own theory on this subject, the authors report their own results. In the first part they study the action of Vitamin K₁ in an alcoholic due to alcohol (60 noncompensated cirrhosis, 20 compensated cirrhosis). When the cirrhosis is compensated, Vitamin K₁ causes a rapid normalization of the prothrombin level, while it does not act at all when the cirrhosis is not compensated.

In a second part, several cases with different liver diseases (hepatitis, cancer, nonthylic cirrhosis) are described. Whenever the integrity of liver cells could be proved by biological tests, Vitamin K₁ improved the level of prothrombin; but whenever biological investigations showed

that the liver cell had been severely damaged, Vitamin K₁ did not modify the prothrombin level.

This study allows a better statement of the therapeutical use of Vitamin K₁. Two conditions seem to be necessary: the decrease of prothrombinemia, the integrity of liver cells. Thus Vitamin K₁ is indicated during the first weeks of obstructive icterus, in the early stages of cirrhosis as well as in nonmiliary hepatic metastases from various primary cancers. Vitamin K₁ is not effective in noncompensated cirrhosis, in hepatitis with jaundice in which liver cells are very altered, in the last stages of obstructive icterus or in miliary liver metastases.

RELATION OF FIBROSIS OF THE PANCREAS TO FATTY LIVER AND/OR CIRRHOSIS: Edward E. Woldman, David Fishman and Abraham J. Segal. J.A.M.A. 169:1281 (21 March), 1959.

During the past 35 years it has been observed that fatty infiltration of the liver followed by fibrosis occurs in the presence of pancreatic disease, be it pancreatic lithiasis, pancreatic fibrosis, carcinoma of the pancreas or diffuse pancreatic disease.

During 1,000 autopsies, 234 cases of pancreatic fibrosis were observed with 117 showing fatty liver, 32 fatty liver and cirrhosis and 7 cirrhosis alone for a total of 156 cases or 66.6 per cent, 78 showed no liver involvement.

Fibrosis of the pancreas occurs in alcoholics and those suffering from biliary tract disease, which would indicate some nutritional factor responsible but evidence seems to point to the pancreas as the original instigator of its own fibrosis for in a series of 32 alcoholics with proved pancreatic calcification, no gallstones or gall-bladder disease was found.

It seems that large amounts of alcohol plus gastric hydrochloric acid when passed into the duodenum, causes a spasm of the sphincter of Oddi with obstruction to passage of pancreatic fluid. This influences the pancreas to secrete extra fluid under pressure that could rupture the finer radicles of the pancreatic tree setting up inflammation leading to chronic pancreatitis.

Intravenous alcohol to the point of intoxication produces no such effect upon the pancreas.

Pancreatic insufficiency results in lessening of digestion, especially protein, with a lowering of choline and other lipotropic substances and a deficiency of phospholipid synthesis, a failure of fat transportation and oxidation with lipid accumulation in the liver, with resulting fatty liver followed by fibrosis of that organ.

J. EDWARD BROWN

ORAL CHOLANGIOGRAPHY: J. Russell Twiss and Lee Gillette. J.A.M.A. 169:1275 (21 March), 1959.

Forty-six patients whose routine cholecystography failed to reveal pathology of gallbladder were given oral multiple doses of iopanoic acid in an attempt to confirm or deny the clinical picture.

The routine was standard—in the evening at 7 P.M., 6 tablets of iopanoic acid were given with a glass of water and a repeat dosage at 7:30 P.M., at 9 P.M. one fluid dram of paregoric was administered

in a glass of water. In the morning at 7 A.M., 6 tablets of iopanoic acid and a glass of water was given, at 9 A.M., 2 fluid drams of paregoric in a glass of water completed medication.

Films of upper abdomen were taken at 10 A.M. and repeated at 11 A.M. In cases where no visualization of ducts occurred, roentgenology was repeated in 24 hours.

Twenty-three cases gave visualization of

gallbladder and ducts with stone, 17 out of 18 operated upon confirmed preoperative diagnosis; 12 showed visualization without stone, of these three were operated upon, 2 for stenosis of common duct sphincter, 1 for acute cholecystitis; 11 showed no visualization of gallbladder, but in 6 the common ducts were visible, 8 of this group were operated upon for cystic duct obstruction. Nine from group 2 were spared surgery.

Jaundice will retard routine cholangiography in impaired hepatic function, catarrhal cholecystitis, cystic duct obstruction

but in 25 per cent of the catarrhal cholecystitis cases, oral iopanoic acid gave normal visualization.

Oral cholangiography has its greatest use in chronic cholecystitis with moderate cystic duct pathology where routine intravenous dye fails, even when stone formation is present and located in the ducts, oral visualization may give more information than intravenous attempts.

The procedure is of immense value in eliminating obscure abdominal symptoms that simulate gallbladder disease.

J. EDWARD BROWN

RESECTION OF LEFT LOBE OF THE LIVER FOR HEPATOMA: James W. Murdoch, Jr. and John C. Lawrence. *Am. Pract. & Digest. Treat.* 10:657 (April), 1959.

The authors present a case report to emphasize the fact that cure is possible for primary cancer of the liver. The surgical treatment of hepatomas of the liver is certainly not a new procedure and the authors quote Keen's report, published in 1899, of 76 cases of resections for liver tumors performed to that date. Warri, in 1945, reported on 570 cases of resections for tumors of the liver and in 1951 Altman reported 68 cases of lobectomies of the left lobe of the liver. Pack, in 1948, successfully resected the right lobe of a liver. The case reported by the authors is a successful left lobectomy in a 63-year old white male, alive and well two years after sur-

gery. In their discussion, the authors mention that 85 per cent of cases of liver tumors are found in males and that carcinoma is more likely to occur in the cirrhotic liver. Symptoms of a liver tumor are not unlike those of a far-advanced carcinoma in the upper abdomen, with pain and weight loss and a large tender liver mass as the principal presenting complaints. Other symptoms such as nausea, vomiting and hemorrhage may also be present. Liver tumors may present themselves as an acute upper abdominal inflammatory syndrome.

JULES D. GORDON

INFECTIOUS HEPATITIS IN CLEARFIELD COUNTY, PENNSYLVANIA: I. A PROBABLE WATER-BORNE EPIDEMIC: J. W. Mosley, W. D. Schrack, T. W. Densham and L. D. Matter. *Am. J. Med.* 26:555 (April), 1959.

An epidemic of infectious hepatitis occurred in Curwensville, Clearfield County, Pennsylvania, in March 1956. One hundred twenty-nine cases occurred in Curwensville and an additional 40 in the surrounding School Jointure during a 39-day period. Investigation revealed time, age and geographic characteristics which sug-

gest common source rather than contact transmission. The peculiarities of the municipal water supply fit the epidemiologic data to make this the probable vehicle. This was an epidemiological study rather than a clinical evaluation of the epidemic.

JOHN M. McMAHON

FATTY INFILTRATION OF THE LIVER: James W. Hurley and Kenneth L. Partlow, II. *Northwest Med.* 58:711 (May), 1959.

The authors discuss the diagnosis and treatment of fatty infiltration of the liver. The differential diagnosis chiefly concerns cirrhosis. They consider that at present, biopsy is the only reliable method of differentiation, but suggest that a study of

estrogen excretion might be worthwhile investigating for possible differential value. There are apt to be more negative tests in fatty liver than in cirrhosis, but this is not in itself of differential value. In their nine cases, if one case with jaundice is excluded

ed, the tests were as follows: Reversal of albumin/globulin ratio, none; anemia, one case; elevated bromsulfalein retention, 2 cases; prothrombin time between 49 and 75 per cent; cephalin flocculation all normal; bilirubin and alkaline phosphatase all normal.

There was excessive alcohol intake and decreased dietary intake; right upper quadrant pain in three patients; no weight loss in any; patients were usually obese; vascular spiders present in four; Palmer erythema in six, testicular atrophy in 2 cases.

Since the condition may eventuate in cirrhosis, treatment is desirable; it consisted in abstinence from alcohol, high caloric diet, with no special emphasis on proportion of fat and protein. Supplemental lipotrophin and vitamins were not used. Testosterone appeared to be of no value. The liver returned to normal size in all; average time 3.4 months; longest 12 months. Impotence cleared up in 1.5 months. Palmer erythema did not clear in 7 months; spiders did not change in 4.2 months.

SAMUEL L. IMMERMANN

FAMILIAL NONHEMOLYTIC JAUNDICE WITH CONJUGATED BILIRUBIN IN THE SERUM: A CASE STUDY: Leon Schiff, Barbara H. Billing and Yoichi Oikawa. New England J. Med. 260:1315 (25 June), 1959.

Expanded chemical methods of differentiating conjugated and nonconjugated bilirubin in the serum plus careful observation and the increased use of liver biopsy have separated from congenital hepatic dysfunction (Gilbert's Disease) several distinct clinical entities of which chronic idiopathic jaundice (Dubin-Johnson syndrome) is the most common. Crigler-Najjar syndrome possibly a form of Gilbert's disease is of interest primarily to pediatricians. Recently Rotor and associates described a type of familial non-hemolytic icterus with direct van den

Berg reaction. The authors present another case similar to that of Rotor in which a young Japanese girl with chronic icterus has a serum containing both free and conjugated bilirubin. The liver was histologically normal ruling out Dubin-Johnson syndrome and blood studies showed that this was not hemolytic jaundice. Another case of nonhemolytic jaundice is presented, possibly not as rare as previously thought, which probably represents a familial inborn error of metabolism expressed as a defect in ability to excrete bilirubin.

RALPH D. EICHORN

TORSION OF THE GALLBLADDER: Sadredin Musavi and G. H. Yeager. J.A.M.A. 170:670 (6 June), 1959.

This is a most uncommon condition and rarely diagnosed. Only 113 cases have been reported in the literature since this entity was first described in 1898.

Torsion of the gallbladder is not possible unless the gallbladder is somewhat

anomalous; not in its fossa on the visceral surface of the liver but completely surrounded by peritoneum and lying free in the abdominal cavity or suspended by a mesentery.

IRVIN DEUTSCH

INTRAHEPATIC BILIARY ATRESIA: L. Jerome Krovetz. J. Lancet 79:228 (June), 1959.

Two cases of intrahepatic biliary atresia are reported, making a total of 25 cases reported in the literature to date. One child died at the age of 3 years from hemorrhage. Intrahepatic biliary ducts were completely absent at autopsy. Accumulation of bile pigment was found around the portal areas. Islands of foam-

filled macrophages were also found in the spleen, lungs, heart, abdominal lymph nodes, skin, and bone marrow.

The other case, a 16-year old girl, is in relatively good health except for a severe pruritus. This is the longest time that a patient with biliary atresia has been reported to have survived. The diagnosis

was established by liver biopsy and surgical exploration. Two theories have been advanced concerning the increased longevity by cases of intrahepatic biliary atresia since 1945. Krohulik and co-workers reason that the usual causes of death are related to infections and hemorrhages, and that the advent of antibiotics and Vitamin K has increased the survival rate. Ahrens and associates suggest that the absence of intrahepatic ducts protects the liver paren-

chyma. Microscopic examination of the livers in their cases revealed varying degrees of fibrosis in the portal areas but no localized collections of inflammatory cells suggesting a burned out reaction around previously existing ducts. They postulated that the absence of intrahepatic ducts might limit the amount of pressure damage to the liver cells.

SAMUEL M. GILBERT

WILSON'S DISEASE, PORTAL HYPERTENSION AND INTRAHEPATIC VASCULAR OBSTRUCTION: W. Jape Taylor, F. C. Jackson and Wallace N. Jensen. *New England J. Med.* 260:1160 (4 June), 1959.

Splenic-pulp pressure studies together with hepatic blood flow determinations indicate that the portal hypertension of Wilson's disease is due to intrahepatic vascular obstruction at the presinusoidal level.

From this the authors suggest that in cases of portal hypertension when neither extrahepatic nor intrahepatic lesions are demonstrable a similar site of obstruction may well exist.

A. M. SUSINNO

THE "CALIBRATED" PAPILLOSPHINCTEROTOMY AS A FACTOR OF SUCCESS IN THE SURGICAL TREATMENT OF ANATOMIC AND FUNCTIONAL DISTURBANCES OF ODDI'S SPHINCTER: STANDARDIZED TECHNIC: Antonio Octaviano de Almeida. *J. Internat. Coll. Surgeons* 32:1 (July), 1959.

The author presents a studied review of 26 patients in whom the orifice of the lower end of the common duct was surgically enlarged by papillosphincterotomy. The technic followed was originated by Professor Alves and may be described as a total resection of the papilla of Vater and a partial section of the sphincter of Oddi. An analytical survey following surgery indicated that 24 of the 26 patients obtained

excellent results from the procedure. These 24 patients did not have to have any medication whatsoever following surgery. In one patient the results were good but an antiallergic regimen had to be followed with dietary restrictions. In the one remaining case nausea was associated with occasional headaches and a restrictive diet was imperative.

BERNARD J. FICARRA

HEATSTROKE AND JAUNDICE: R. H. Herman and B. H. Sullivan, Jr. *Am. J. Med.* 27:154 (July), 1959.

A patient who suffered heatstroke and jaundice due to liver disease is described. Upon recovery from the acute phase of his illness the patient demonstrated the following residuals of heatstroke: fatty metamorphosis of the liver, persistent headache, and aching of the extremities relieved only with the ingestion of Seconal. He had an abnormal electrocardiogram.

Of 3,152 cases of hyperpyrexia recorded in the literature, jaundice was found in 186. There were 191 deaths, and jaundice

was present in 14.

Of 244 cases of heatstroke, there was overt jaundice in ten, hyperbilirubinemia only in 13, and of 150 fatalities jaundice was found in only seven cases. Liver damage was found by histological study in 17 cases.

The liver damage of hyperpyrexia is an occasional and serious complication of heatstroke.

JOHN M. McMAHON

ESOPHAGEAL VARICES IN HODGKIN'S DISEASE INVOLVING THE LIVER:R. Levitan, H. D. Diamond and L. F. Craver. *Am. J. Med.* 27:137 (July), 1959.

Two case of Hodgkin's disease with esophageal varices are reported. Both patients had extensive liver involvement with

Hodgkin's disease, and the second patient had, in addition, constrictive pericarditis.

JOHN M. McMAHON

PANCREAS**THE ROLE OF SURGERY IN ACUTE PANCREATITIS: W. Grimes Byerly and Lee Gillette. *Clin. Med.* 6:17 (Jan.), 1959.**

The authors reviewed 126 cases of pancreatitis from the Roosevelt Hospital (N.Y.) from 1939-1955. The article sets forth the diagnostic criteria and classifies the condition as edematous, hemorrhagic (necrotic) or suppurative. The most commonly associated conditions found with pancreatitis are chronic biliary tract disease, in 52 per cent of all cases and alcoholism in 16 per cent. Peptic ulcer, and gastric carci-

noma also complicated pancreatitis and pancreatitis after gastrectomy is not uncommon.

The authors feel that the common channel theory can explain most if not all cases of pancreatitis and the object of surgical treatment is to produce common duct decompression and clear the biliary tree.

IRVIN DEUTSCH

CHRONIC RELAPSING PANCREATITIS: ETIOLOGY AND DIAGNOSIS: Benjamin B. Weisiger. *Am. Pract. & Digest. Treat.* 10:79 (Jan.), 1959.

The disease may involve all or any part of the gland to any degree. Enlargement and palpation may be such as to make a differentiation from carcinoma difficult. The most attractive theory of pathogenesis at present is that of obstruction plus increased secretion. The diagnosis of the acute exacerbation in a majority of the cases may be obtained with the use of routine laboratory tests available in any hospital. The determination of serum amylase is the most valuable single diagnostic test available at present. Elevated values were found in 73 per cent of the patients studied. The determination of serum lipase is a cumbersome test and has little advantage over the serum amylase other than the fact that its

values may persist for 24 to 48 hours longer. The most valuable tests which can be done in any hospital laboratory are the blood sugar and urine sugar determination. Glucose tolerance tests may be of value as 45 per cent of the patients had hyperglycemia or glycosuria. Barium should be given to rule out the presence of a pseudocyst or tumor. Early x-ray studies of the gallbladder are important. Testing the efficiency of the secretion of the pancreas may be done.

Diagnosis of chronic pancreatic impairment may require extensive and complicated studies and they are not too reliable.

I. HENRY EISEL

ACUTE PANCREATITIS: Samuel Walder. *J. Internat. Coll. Surgeons* 31:1 (Jan.), 1959.

Diagnostically and therapeutically acute pancreatitis is a highly controversial disease. Manifestations begin with acute epigastric pain prostration, shock and toxicity. Increase in serum amylase is almost always associated with this disease.

Differential diagnosis should include perforated peptic ulcer, acute appendicitis, cholecystitis and coronary thrombosis. Pa-

tient should receive the necessary antibiotic therapy. When surgery is performed, cholecystectomy or cholecystostomy is indicated. Care should be taken not to perforate the pancreatic capsule.

The author reports one case of acute pancreatitis wherein he performed cholecystostomy and removal of a biopsy specimen of the omentum. Pathological diagnosis was

acute fat necrosis. Patient was fine until 20th postoperative day when he developed bowel obstruction; lysis of adhesions corrected this condition. Patient finally recovered after about four months' observa-

tion. It is interesting to note that this patient with an acute necrotizing pancreatitis was treated successfully by means of surgery.

ABRAHAM BERNSTEIN

EXPERIMENTAL PANCREATITIS—RECENT CONTRIBUTIONS: Morton I. Grossman. *J.A.M.A.* 169:1567 (4 Apr.), 1959.

All forms of experimental pancreatitis resemble the human disease. However, caution must be exercised in the evaluation of the pathogenesis of human pancreatitis on the basis of animal experiments. The common channel theory of Opie postulating a reflux of bile into the pancreatic ducts has many adherents in spite of the fact that such reflux has never been demonstrated by intravenous cholangiography. Only in the presence of an intraductal pressure high enough to rupture the acini or during an exceedingly high enzyme contents can it produce pancreatitis. The other popular theory is that of pancreatic duct obstruction. A remarkably high pressure is already present in the pancreatic ducts during fasting in normal persons. Various foods and

especially alcohol may elevate this pressure moderately but not greatly. Ischemia produced by thromboembolism, vascular disease or the Schwartzman and Arthus phenomena may cause fulminating pancreatitis. Lesser degrees of vascular impairment may produce damage of the gland in the presence of obstruction. The activation of pancreatic enzyme within the pancreatic tissue may also produce pancreatitis. If this occurs in humans is not certain. However, an increase of proteases is seen during an acute attack and may be responsible for shock. As the blood has powerful antitryptic and antichymotryptic activity, one must assume that great quantities of enzyme are liberated.

H. B. EISENSTADT



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PATHOLOGY AND LABORATORY RESEARCH

MOLISCH-POSITIVE MUCOPOLYSACCHARIDES OF GASTRIC CANCERS AS COMPARED WITH THE CORRESPONDING COMPONENTS OF GASTRIC MUCOSAE: SECOND AND THIRD REPORTS: Hiroya Kawasaki. *Tohoku J. Exper. Med.* 68:119 and 173 (25 Aug.), 1958.

These two papers are follow-ups of a previous publication describing the preparation and the physical, chemical and biological properties of two groups of mucopolysaccharides obtained from normal gastric mucosae and from gastric cancers. These substances were found to behave very similar in cancer as well as noncancer

cases. However, some differences were noticed in the blood group A and B activity, with sialic acid contents, the optical rotation of sodium light and the molecular weight. The significance of these findings remains to be established.

H. B. EISENSTADT

THE EFFECTS OF PHENYLBUTAZONE AND ACTH ON GASTROINTESTINAL MUCOSA: Joseph T. Freeman, M. A. Geiss and Roberta Hafkesbring. *Am. J. M. Sc.* 237:67-73 (Jan.), 1959.

Two clinical case reports are given of peptic ulceration in patients given phenylbutazone and ACTH. This led the authors to experimentation with guinea pigs, using these drugs singly or in combination in 80 adult guinea pigs, using 18 as controls. Half of these animals developed peptic ul-

cers when given ACTH or phenylbutazone, or both, with a slightly higher incidence in those animals receiving phenylbutazone. It is suggested that where these drugs must be used, protection of the gastric and duodenal mucosa is essential.

BERNARD FARFEL

MOLISCH-POSITIVE MUCOPOLYSACCHARIDES OF GASTRIC CANCERS AS COMPARED WITH THE CORRESPONDING COMPONENTS OF GASTRIC MUCOSAE: FOURTH REPORT: Hiroya Kawasaki. *Tohoku J. Exper. Med.* 69:153 (25 Feb.), 1959.

Mucopolysaccharides (MPS) were prepared from human gastric cancers and from noncancerous gastric mucosae. Their properties were compared within each of the following blood groups: A; AB; B; and O. Differences between cancer MPS and noncancer MPS within each blood group

were partly marked, partly only minute. Differences were found in blood group potency; sialic acid content; glucosamine/galactosamine ratio; optical rotation; molecular axial ratio and molecular weight.

WALTER CANE

ROLE OF EXFOLIATIVE CYTOLOGY IN THE DIAGNOSIS OF CANCER OF THE DIGESTIVE TRACT: Howard F. Raskin, Joseph B. Kirsner and Walter L. Palmer. *J.A.M.A.* 169:789 (21 Feb.), 1959.

Microscopic studies of exfoliative epithelial cells have been made from all accessible body cavities but the diagnostic or screening value derived has varied from reports published by many investigators.

In this paper according to the methods employed by the authors the diagnostic yield of exfoliative cytology of the gastrointestinal tract has proven second only to direct biopsy.

In 95 per cent of a large number of cases of carcinoma of the esophagus, stomach and colon the results of exfoliative cytology were positive. False positives were infrequent for the esophagus and stomach and none were recorded for the colon.

The pancreatic and biliary system proved the most difficult area for testing and interpretation but even here there is a 60 per cent detection of malignant cells.

Only two false positives of 301 patients without carcinoma were found in this grouping.

Confusing cells were encountered in healing gastric ulcers, atrophic gastritis,

gastric polyps and benign granulomas. Sarcomas and leiomyomas failed to slough any characteristic cells.

A. M. SUSINNO

TOXIC SUBSTANCES IN CANCER: VI. EFFECT ON THE MOVEMENT OF PARAMECIUM OF THE EXTRACT OF GASTRIC CARCINOMA TISSUE (SECOND REPORT): Iwao Yamaguchi, Hisashi Kamma and Kiyota Oh-Uti. *Tohoku J. Exper. Med.* 69:185 (25 Feb.), 1959.

In a previous paper the authors had reported on the interesting observation that aqueous extract of gastric carcinoma tissue inhibits the movements of infusoria called paramecium, and that a basic substance of low molecular weight is responsible for this effect. The present communication presents the results obtained from investigations on the extracts of gastric carcinoma tissue in organic solvents. Identical tests were made on extracts obtained from

gastric mucosa of the same cancer patients but away from the carcinomatous lesion and also on gastric mucosa of noncancerous patients. Alcohol extract, acetone extract, and their fractions, of carcinomatous tissue inhibited the movement of paramecium more intensely than those from control tissue. Most effective was a fraction consisting of fatty acid whose lithium salt is insoluble in 50 per cent alcohol.

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1. *British Medical Journal* 2:827, 1955

2. *American Journal of Gastroenterology* 28:439, 1957

NUCLEIC ACIDS: XI. COMPARISON OF DNA FROM GASTRIC CANCER WITH THAT FROM GASTRIC MUCOSA: Sin-iti Abe. Tohoku J. Exper. Med. 69:143 (25 Feb.), 1959.

The various properties of deoxyribonucleic acid (DNA) have become the center of interest in cancer research. Interpretation of these variations, however, has just begun. The author found more differences than other researchers between DNA in normal tissue and DNA in cancerous tissue. The reason for the discrepancy is the fact that the author included in his studies not only the chemical properties of DNA but physical and biological properties as well. He found differences in the amount

of certain amino acids between cancer DNA and normal mucosa DNA (less adenine and guanine but more cytosine). Cancer DNA absorbs ultraviolet light more strongly than noncancerous DNA. Cancer DNA is less dextro-rotatory than noncancerous DNA. Cancer DNA gives stronger skin reactions in cancer patients than in noncancer patients. Also of interest was a more intensive Schiff reaction in cancer DNA.

WALTER CANE

BLOOD AMMONIA CONCENTRATION AND BROMSULFALEIN RETENTION IN UPPER GASTROINTESTINAL HEMORRHAGE; Gerald A. Belkin and Harold O. Conn. New England J. Med. 260:530 (12 March), 1959.

The authors have made a study of the blood ammonia and bromsulfalein retention in 96 patients with massive upper gastrointestinal hemorrhage in order to determine the site of bleeding. Blood, like other nitrogenous substances in the alimentary tract, undergoes bacterial enzymatic degradation during which ammonia is liberated. In patients without hepatic disease the ammonia is removed from circulation as the portal blood passes through the liver. In cirrhotic patients much of the blood is diverted around the liver by way of portasystemic anastomoses and thereby increasing blood ammonia concentration.

There were 36 cirrhotic of the 96. The site of bleeding was considered proved when it was demonstrated by esophagoscopy, gastroscopy, x-ray, laparotomy or autopsy. The authors used 15 per cent as the lower limit for bromsulfalein retention

to allow for shock and 150 mcg. per 100 c.c. as the upper limit of normal for blood ammonia. Bromsulfalein retention was greater than 15 per cent in 34 of the 36 (93 per cent) cirrhotic, and in 15 of the 60 (25 per cent) noncirrhotic patients. The blood ammonia levels were within normal limits in 57 of the 60 (95 per cent) patients without cirrhosis and were elevated in 26 of the 36 (87 per cent) cirrhotics. Six of the cirrhotics with normal ammonia levels had received antibiotics capable of depressing blood ammonia concentrations.

The concurrence of elevated blood ammonia and bromsulfalein levels were considered practically diagnostic of cirrhosis. The tests were of no diagnostic value if either determination was elevated and the other normal.

SAUL A. SCHWARTZ

PHYSIOLOGIC OBSERVATIONS UPON A PARTIAL PANCREATIC FISTULA FOLLOWING GASTRECTOMY; Marion C. Anderson, W. Harrison Mehn and Harold L. Method. Am. J. Surg. 97:260 (March), 1959.

Pancreatic fistula, although infrequent, constitutes a serious complication of gastric surgery, and may be expected to increase with the evolution of more radical surgical approaches to neoplasms of the stomach, biliary tract, and pancreas. Much of the present knowledge of pancreatic exocrine function is derived from the results of animal experimentation. In man, external pancreatic fistulas provide an opportunity to evaluate pancreatic function directly.

A case study of a 42-year old male with a pancreatic fistula following subtotal gastrectomy is given in detail.

Extensive studies were done which included volume, chemical determinations, electrolytes, enzymes and pH. Detailed studies were also done of the effect of various stimuli on pancreatic secretion. Digestive studies using I^{131} labeled "Triolein" and I^{131} labeled "Human Serum Albumin" were carried out. Diversion of

gastric contents from the duodenum to the jejunum by gastrojejunostomy did not appear to alter the normal volume response from the pancreas when secretin or agents which initiate the release of secretin were administered.

The results suggest that a differentiation between volume and electrolyte stimula-

tion (secretin effect) and enzyme stimulation (pancreozymin effect) previously demonstrated in experimental animals, also exists in man. Billroth II gastrectomy did not appear to alter either pancreatic or digestive function to any significant degree in this patient.

CARL J. DePRIZIO

I¹³¹-THYROIDAL UPTAKE IN CIRRHOSIS: STUDY OF 30 CASES: Y. Boquien and J. Guenel. Sem. Hop. Paris 35:935-937 (March), 1959.

Twenty-four hours intake of I¹³¹ was measured in 30 cases of alcoholic cirrhosis. Many patients had clinical symptoms of endocrine insufficiency: scarce axillary and pubic hair, dry skin, amenorrhea. . . . However 2 patients showed intakes greater than normal (up to 89 per cent), although they had no clinical evidence of hyperthyroidism. There was no relationship between intake and any of the following: presence or absence of ascites, degree of hepatic test disturbance, total plasma pro-

tein level. Abnormal fixation of I¹³¹ in cirrhosis cannot be accounted for by iodine deficiency nor by Prednisone treatment that most patients received. Although plasma total protein level seems to play no role in thyroidal intake it is possible that low level of certain protein components (albumin and α globulins experienced by paper electrophoresis) causes a decrease of protein-bound iodine and consequently raises pituitary excretion of TSH.

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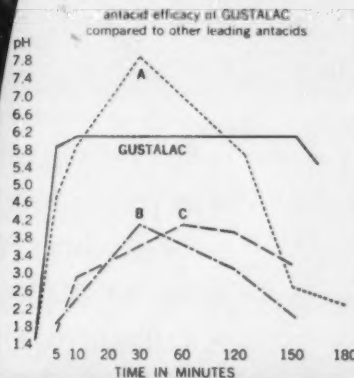
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1. Kirstner, J. B.: J.A.M.A. 166:1727, 1958.



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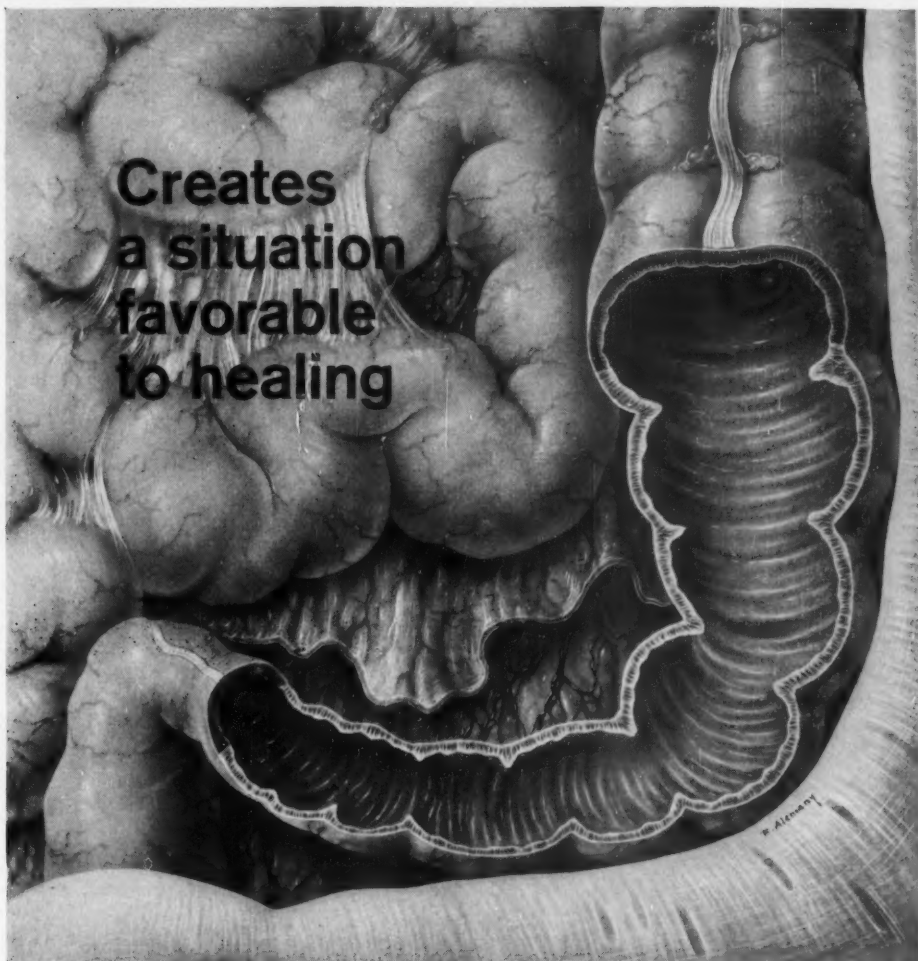
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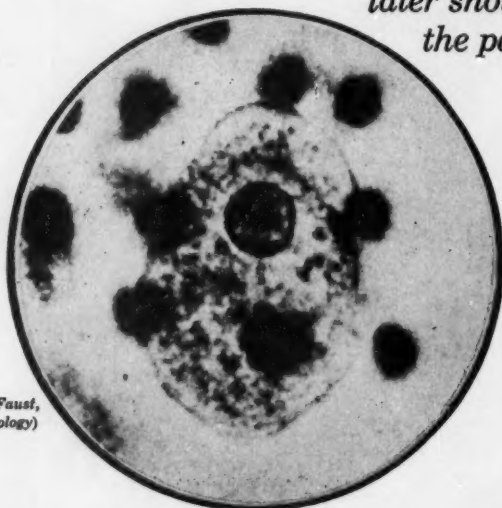
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1. Frye, W.W., and Lampert, R.: Treatment of Asymptomatic *Endamoeba histolytica* Carriers with a Formulation of Bacitracin-Methylene Disalicylate and Iodochlorhydroxyquin (Anameba). *Am. J. Gastroenterol.* 34:429-432 (Oct.), 1960.

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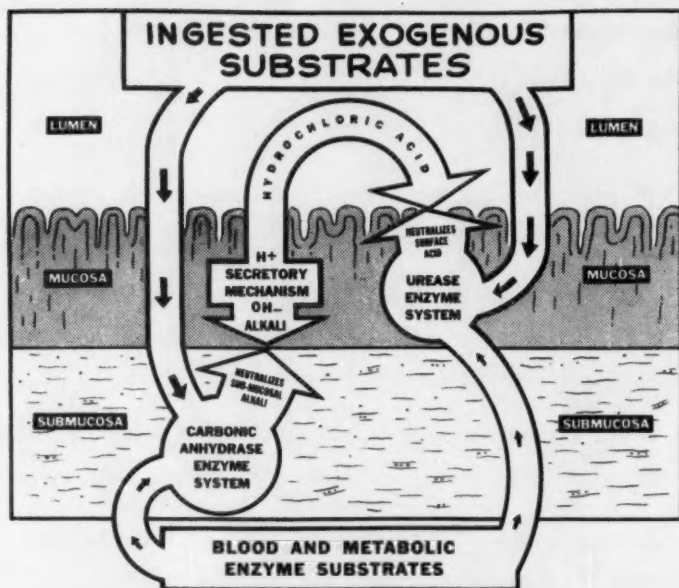
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- (1) Goodfriend, Vanderkleed & Goodfriend. "Enzymatic Therapy of Peptic Ulcer and Digestive Disorders." *American Journal Gastroenterology*, Vol. 33, No. 1, Pgs. 80-89, January 1960.
- (2) Kelly, H. T., M. D., "Treatment of Gastrointestinal Ulcer and Certain Digestive Disorders with Mucosal Enzyme Substances", *American Journal of Gastro.*, Vol. 33, No. 12, December, 1960.



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1. Nesselrod, J. P.: *Clinical Proctology*, ed. 2, Philadelphia, Saunders, 1957. 2. Page, S. G., Jr., et al.: *J. A. M. A.* 157:1208, Apr. 2, 1955. 3. Gross, J. M.: *J. Internat. Coll. Surgeons* 23:34, Jan., 1955. 4. Page, S. G., Jr., et al.: *Gastroenterology* 32:747, Apr., 1957. 5. Heilman, L. D.: To be published.

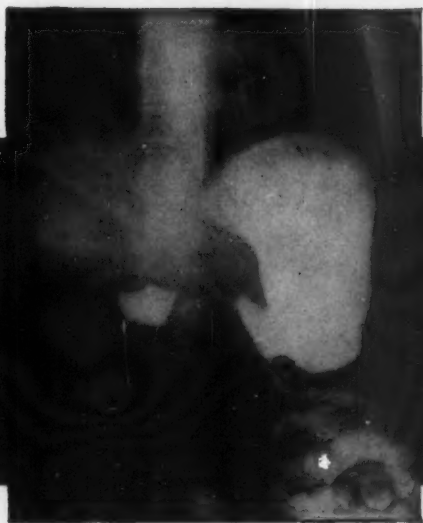
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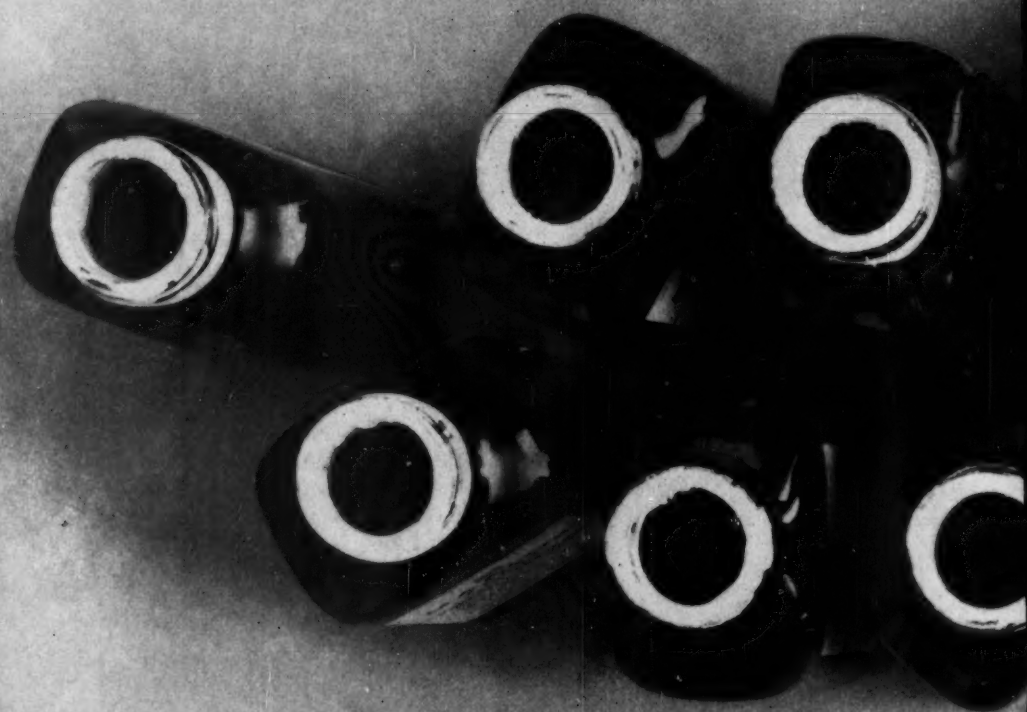
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Dosage: 1 tablet t.i.d. at mealtime and 2 at bedtime.

Milpath-200 — Yellow, coated tablets of 200 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride. Bottle of 50.

Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

Milpath®

•Miltown + anticholinergic

WALLACE LABORATORIES Cranbury, N. J.

1579



don't forget...

- to correct abnormal bowel function (either constipation or non-specific diarrhea)
- eliminate the high roughage foods containing irritating bulk (lignin and cellulose)
- and replace them with

KONSYL
(the bowel normalizer of choice)



*Your Patients
will appreciate
the modest cost!*

Konsyl supplies a non-irritating bulk consisting entirely of hemicelluloses derived from blond psyllium. The smooth bulk of Konsyl disperses with the intestinal contents to create a soft-formed, easily passed stool. Konsyl assures the resumption of a normal peristaltic pattern and contains no sugar or other diluents.

Made by BURTON, PARSONS & COMPANY, Since 1932
Originators of Fine Hydrophilic Colloids
Washington 9, D. C.

The
principle
that makes

a duck
sink...



produces soft,
normal stools
in functional
constipation

SURFak®

Water doesn't roll off this duck's back... because the water is Surfak-treated. Surfak decreases interfacial tension between water and oil... penetrates the natural oils in the feathers, permits water absorption, adding weight so that the duck sinks.

Similarly, in functional constipation, Surfak quickly permeates the heterogeneous fecal mass. The superior surfactant action of calcium bis-(dioctyl sulfosuccinate) reduces the interfacial tension between the aqueous and lipid phases of the intestinal content to minimal values. The result is soft homogeneous feces which are easily moved to evacuation, naturally.

DOSAGE:

Adults: One 240 mg. Surfak capsule daily.
Children (and adults with minimal needs):
One to three 50 mg. Surfak capsules daily.

SUPPLIED:

240 mg. Surfak capsules in bottles of 15 and 100. 50 mg. Surfak capsules in bottles of 30 and 100.

LLOYD BROTHERS, INC.

CINCINNATI 3, OHIO

